Chemistry

ABSTRACT

J.J. Whiting
Ph.D. 1970

PART A - CHEMISTRY OF N-S AND N-O BONDS

The compounds prepared by Tercinet from the reaction of various alkaloids with silver sodium thiosulfate have been shown to have N-ammonium-S-thiosulfate structures. Possible mechanisms of their formation and hydrolysis are discussed. Tertiary amines react with sodium dithionate to give amine-sulfur trioxide complexes (substituted sulfamic acids).

Amine oxides react with sulfur dioxide to give either sulfitoamines, or substituted sulfamic acids, or reduction to the tertiary amine, or dealkylation to secondary amine and aldehyde in a Polonovski-type reaction, or variously substituted sulfonic acid products. The particular pathway is dependent on amine oxide structure, temperature and solvent. The reactions of sulfur dioxide with hydroxylamine and β-phenylhydroxylamine under various conditions have also been studied.

Sulfatoamines, formed by reaction of amine oxides with pyridine-sulfur trioxide complex, are hydrolyzed by aqueous alkali to the corresponding amine oxide and sulfate ion.

PART B - RING-CHAIN TAUTOMERISM OF HYDROXYKETONES

A study of the UV, IR, and NMR spectra of 5-hydroxy-2-pentanone and of 6-hydroxy-2-hexanone has shown that in most organic solvents there is a slight preference for the open-chain form of the hydroxyketone over the cyclic hemiketal. Increase in temperature and highly polar organic solvents favor the open-chain tautomer; in water there was no evidence of any

CHEMISTRY OF N-S AND N-O BONDS, RING-CHAIN TAUTOMERISM

PART A

THE CHEMISTRY OF COMPOUNDS CONTAINING N-O AND N-S BONDS

PART B

RING-CHAIN TAUTOMERISM OF HYDROXYKETONES

by

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PART A

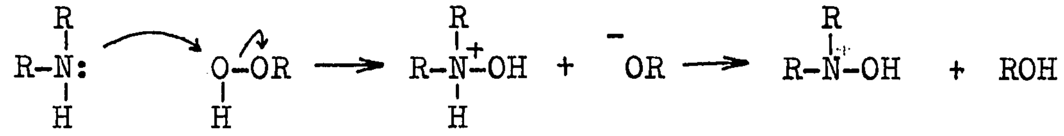
The Chemistry of Compounds Containing N-O and N-S Bonds

INTRODUCTION

PREFACE

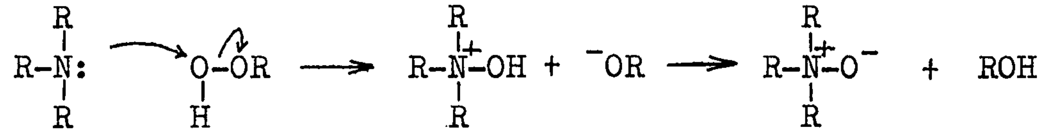
Part A of this thesis is made up of five chapters concerned with the chemistry of compounds containing the N-O and the N-S linkage; Part B of one chapter concerned with the ring-chain tautomerism of hydroxyketones. Each chapter is written in the form of a paper which has been published or will be submitted to the Canadian Journal of Chemistry.

Compounds containing the N-O linkage have long been known, and are relatively stable. The oxidation of secondary amines with peroxides leads (although in bad yields, because of further oxidation) to substituted hydroxylamines (1):

[1] 

$$R\text{-}\underset{H}{\overset{R}{\ddot{N}}} + \underset{H}{O}\text{-}OR \longrightarrow R\text{-}\underset{H}{\overset{R}{\overset{+}{N}}}\text{-}OH + {}^{-}OR \longrightarrow R\text{-}\overset{R}{N}\text{-}OH + ROH$$

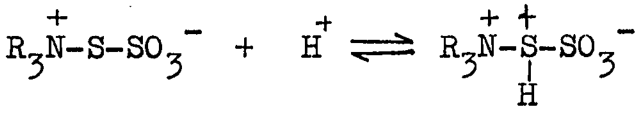
and of tertiary amines to amine oxides (2):

[2] 

$$R\text{-}\underset{R}{\overset{R}{\ddot{N}}} + \underset{H}{O}\text{-}OR \longrightarrow R\text{-}\underset{R}{\overset{R}{\overset{+}{N}}}\text{-}OH + {}^{-}OR \longrightarrow R\text{-}\underset{R}{\overset{R}{\overset{+}{N}}}\text{-}O^{-} + ROH$$

The driving force for these reactions comes in part from the ease of rupture of the O-O bond; H_2O_3, containing a chain of three oxygen atoms is extremely unstable (3).

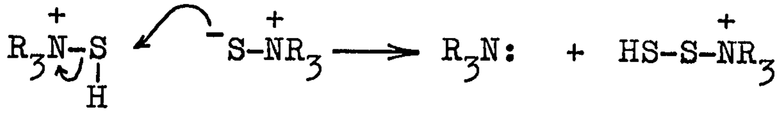
The S-S linkage is much more stable than the O-O linkage (4), but it might be expected that polysulfides would react with amines by reactions analogous to equations 1 and 2. This indeed happens, but the equilibria are less favorable to the formation of products, and the products are much less stable (5). The simple thio analogue $R_3\overset{+}{N}\text{-}S^-$ of amine oxides is not known, although compounds $R_2N\text{-}(S)_n\text{-}S^-$ (n=0-5) are known (6). There is some evidence in Chapter 1 that $R_3\overset{+}{N}\text{-}S^-$ may be spontaneously unstable, decomposing to the amine and elemental sulfur (S_8):

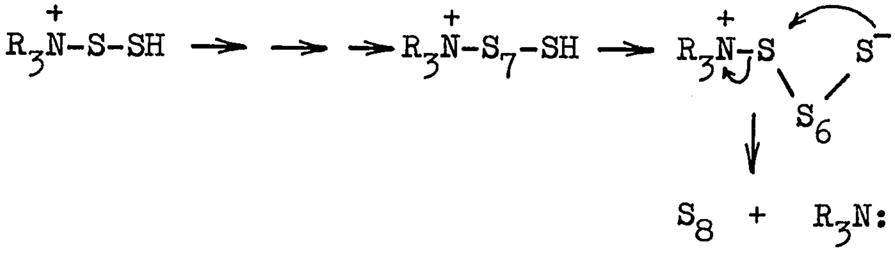
[3] 

$$R_3\overset{+}{N}\text{-}S\text{-}SO_3^- + \overset{+}{H} \rightleftharpoons R_3\overset{+}{N}\text{-}\underset{H}{\overset{+}{S}}\text{-}SO_3^-$$

$$R_3\overset{+}{N}-\underset{H}{S}-SO_3^- \longrightarrow R_3\overset{+}{N}-SH + SO_3$$

$$R_3\overset{+}{N}-SH \rightleftharpoons R_3\overset{+}{N}-S^- + H^+$$





Sulfenamides (H_2N-S-R), the sulfur analogues of O-alkyl hydroxylamines (H_2N-O-R) are known, but the lesser stability of the N-S (as compared with the N-O) bond is evident from the different modes of hydrolysis (7,8):

[4] $$R_2N-O\vdots R' \xrightarrow[190^\circ]{H_3O^+} R_2N-O-H + HO-R'$$

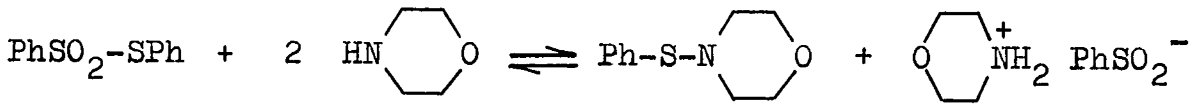
[5] $$R_2N\vdots S-R' \xrightarrow{H_3O^+} R_2NH + [R-S-OH]$$

$$\downarrow$$

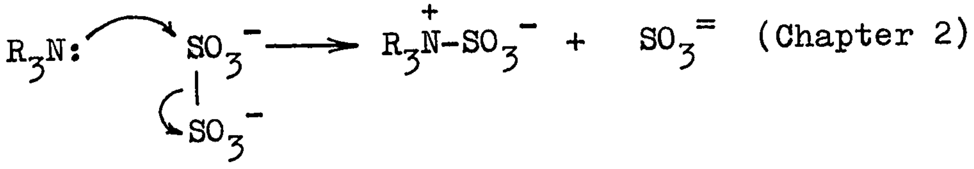
$$RSH,\ RSO_3H,\ etc.$$

Furthermore, R_2N-OR' is inert to the usual nucleophiles, while R_2N-SR' is reactive, as shown by the reversibility of the reaction (9):

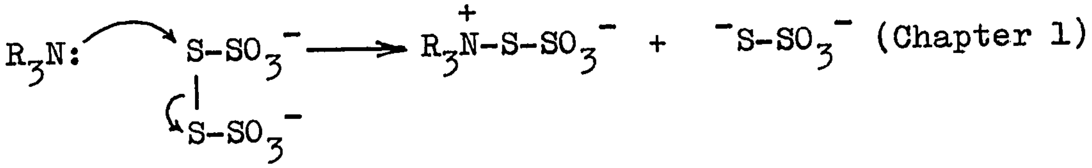
[6]



The stability of the N-S linkage is increased by the attachment to the sulfur of electron-withdrawing groups, so that N-S compounds can be prepared by reactions 7 and 8 (analogous to reaction 2):

[7] 

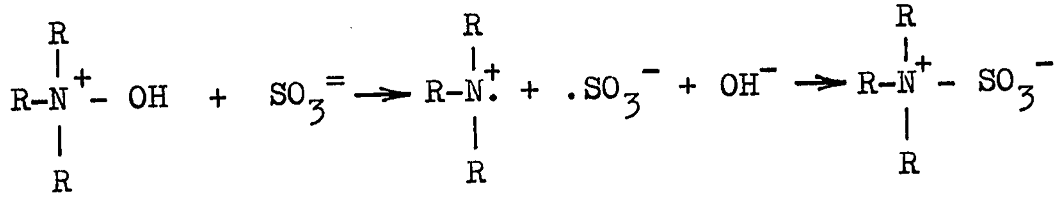
$$R_3N: + \underset{\textstyle SO_3^{-}}{\overset{\textstyle SO_3^{-}}{|}} \longrightarrow R_3\overset{+}{N}\text{-}SO_3^{-} + SO_3^{=} \quad \text{(Chapter 2)}$$

[8] 

$$R_3N: + \underset{\textstyle S\text{-}SO_3^{-}}{\overset{\textstyle S\text{-}SO_3^{-}}{|}} \longrightarrow R_3\overset{+}{N}\text{-}S\text{-}SO_3^{-} + {}^{-}S\text{-}SO_3^{-} \quad \text{(Chapter 1)}$$

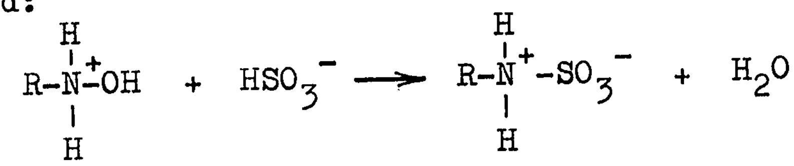
The zwitterions $R_3\overset{+}{N}\text{-}S\text{-}SO_3^{-}$ represent a new class of compounds, and are described in Chapter 1.

Finally, Chapters 3- 5 describe the reactions of some N-O compounds with sulfur dioxide and sulfur trioxide. In Chapter 3 it is shown that the transformation of amine oxides into substituted sulfamic acids by aqueous sulfur dioxide probably involves the free-radical mechanism:

[9] 

$$R\text{-}\underset{R}{\overset{R}{N^{+}}}\text{-}OH + SO_3^{=} \longrightarrow R\text{-}\underset{R}{\overset{R}{N^{+}\cdot}} + \cdot SO_3^{-} + OH^{-} \longrightarrow R\text{-}\underset{R}{\overset{R}{N^{+}}}\text{-}SO_3^{-}$$

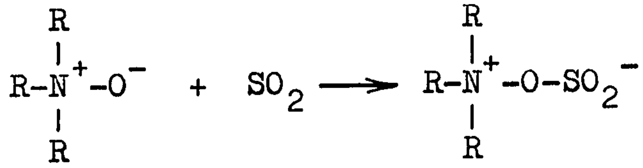
The corresponding reaction of substituted hydroxylamines might be expected to proceed by a similar route, but in Chapter 4 no evidence for free-radical intermediates could be found:

[10] 

$$R\text{-}\underset{H}{\overset{H}{N^{+}}}\text{-}OH + HSO_3^{-} \longrightarrow R\text{-}\underset{H}{\overset{H}{N^{+}}}\text{-}SO_3^{-} + H_2O$$

In anhydrous solvents, sulfur dioxide reacts with amine oxides to form sulfitoamines (10):

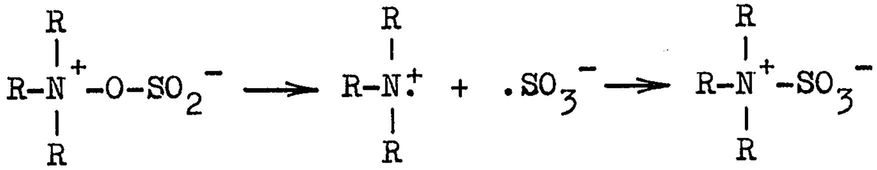
[11]



$$\text{R-}\underset{\text{R}}{\overset{\text{R}}{\text{N}}}{}^{+}\text{-O}^{-} + \text{SO}_2 \longrightarrow \text{R-}\underset{\text{R}}{\overset{\text{R}}{\text{N}}}{}^{+}\text{-O-SO}_2{}^{-}$$

Under certain conditions (as described in Chapter 3) these can rearrange to sulfamic acids, again by what is most probably a free-radical mechanism:

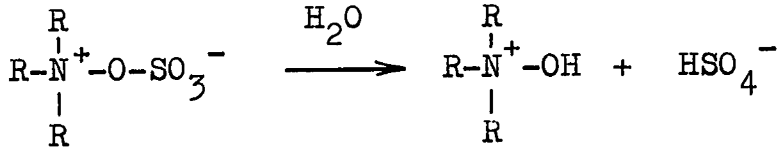
[12]



$$\text{R-}\underset{\text{R}}{\overset{\text{R}}{\text{N}}}{}^{+}\text{-O-SO}_2{}^{-} \longrightarrow \text{R-}\underset{\text{R}}{\overset{\text{R}}{\text{N}}}{}^{\dot{+}} + {}\cdot\text{SO}_3{}^{-} \longrightarrow \text{R-}\underset{\text{R}}{\overset{\text{R}}{\text{N}}}{}^{+}\text{-SO}_3{}^{-}$$

The corresponding sulfatoamines are much more stable, and in water are hydrolyzed back to amine oxides (Chapter 5):

[13]



$$\text{R-}\underset{\text{R}}{\overset{\text{R}}{\text{N}}}{}^{+}\text{-O-SO}_3{}^{-} \xrightarrow{\text{H}_2\text{O}} \text{R-}\underset{\text{R}}{\overset{\text{R}}{\text{N}}}{}^{+}\text{-OH} + \text{HSO}_4{}^{-}$$

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CHAPTER 1

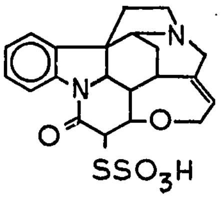
N-AMMONIUM-S-THIOSULFATE ZWITTERIONS FROM ALKALOIDS AND TERTIARY AMINES

ABSTRACT

The compounds prepared by Tercinet (1) from the reaction of various alkaloids with silver sodium thiosulfate have been shown to have N-ammonium-S-thiosulfate structures; they are better prepared by reaction of the alkaloids with sodium tetrathionate. Possible mechanisms of their formation and of their hydrolysis with acid or alkali are discussed briefly.

Les composés préparés par Tercinet (1) par la réaction de differentes alcaloides avec la thiosulfate mixte d'argent et de soude sont montrés d'avoir la structure des N-ammonium-S-thiosulfates. Une meilleure méthode de préparation se fait par la réaction des alcaloides avec la tetrathionate de soude. Le mécanisme de cette réaction, ainsi que celui de l'hydrolyse de ces composés par acide et par alcalie, ont été discutés.

In 1944 André Tercinet (1) described the reaction of silver sodium thiosulfate ($Ag_2S_2O_3 \cdot 2Na_2S_2O_3$) with strychnine, brucine, quinine and harmine to give crystalline solids. He formulated these compounds as S-thiosulfate esters, the compound from strychnine, for example, being assigned the structure 1.



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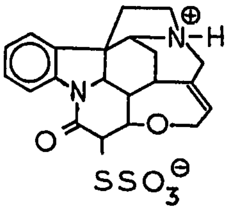


2

Such a compound would be more plausibly formulated as 2, a zwitterionic Bunte salt (2,3). Silver ion is reduced to metallic silver in the reaction, and the overall reaction finds analogy in the formation of a zwitterionic Bunte salt from the oxidation of a mixture of N,N-dimethyl-1,4-phenylene diamine and sodium thiosulfate with dichromate (4,5).

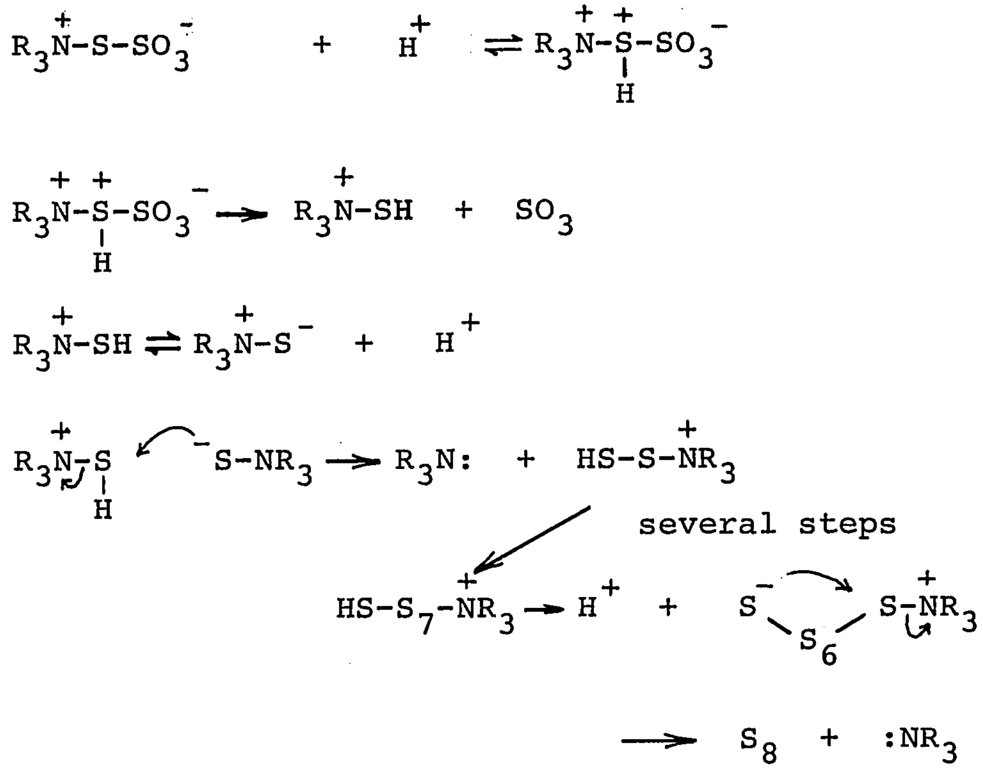
We were led to reinvestigate Tercinet's reaction because of the great usefulness of Bunte Salts in synthesis (5), and because of the potential use of such compounds as anti-radiation agents (6,7). However, while we obtained products having the composition and physical properties reported by Tercinet, we observed them to have, in many cases, different reactions, and in all cases we have shown his structures to be incorrect.

Tercinet obtained the same products, although in smaller yields, by heating the alkaloids with sodium thiosulfate and hydrogen peroxide; we have obtained them by substituting ferric chloride, mercuric oxide, or iodine for hydrogen peroxide. All of these oxidizing agents convert thiosulfate ion ($^{\ominus}S - SO_3^{\ominus}$) to tetrathionate ion ($^{\ominus}O_3S - S - S - SO_3^{\ominus}$), presumably via the radical $\cdot S - SO_3^{\ominus}$ (8a), and Tercinet's compounds are obtained most simply by reaction of the alkaloids with sodium tetrathionate, which was probably the effective reagent in his reactions. When a stream of oxygen is bubbled through a mixture of an alkaloid and silver sodium thiosulfate, little or none of Tercinet's product is obtained, the oxygen acting as a scavenger for $\cdot S - SO_3^{\ominus}$; however, the stream of oxygen has no effect on the yield of product from the alkaloid and sodium tetrathionate.

Sodium tetrathionate is the reagent of choice. It reacted with strychnidine to give a compound $C_{21}H_{24}N_2O_4S_2$ whose structure is discussed below. Tercinet failed to obtain any product from the reaction of strychnidine with silver sodium thiosulfate, perhaps because of the known sensitivity of strychnidine to oxidizing agents (9).

Tercinet's products do not behave like Bunte salts. Thus they do not react with iodine, known to convert Bunte salts to disulfides (10). Furthermore, Tercinet reported that his compound $C_{21}H_{22}N_2O_5S_2$ from strychnine was converted by sodium amalgam in alkaline solution back to strychnine, and not to a thiol, which would be expected. A thiol, along with sulfate ion, would also be expected from the acid hydrolysis of a Bunte salt. Instead, we have found that the hydrolysis of the strychnine product with 6N hydrochloric acid yields strychnine, sulfur, and sulfate ion in essentially quantitative yields. All of this evidence points to a linkage of the S - SO_3^- group to nitrogen and not to carbon, since an N-S linkage can be broken by hydrolysis (11).

A possible mechanism for the acid-catalyzed hydrolysis is:



[1] $R_3\overset{+}{N}-S-SO_3^- + H^+ \rightleftharpoons R_3\overset{+}{N}-\underset{H}{\overset{+}{S}}-SO_3^-$

[2] $R_3\overset{+}{N}-\underset{H}{\overset{+}{S}}-SO_3^- \rightarrow R_3\overset{+}{N}-SH + SO_3$

[3] $R_3\overset{+}{N}-SH \rightleftharpoons R_3\overset{+}{N}-S^- + H^+$

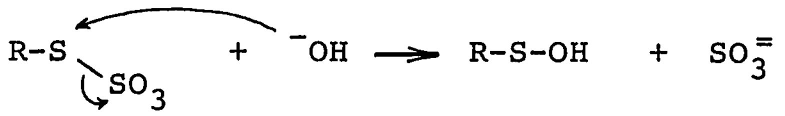
[4] $R_3\overset{+}{N}-\underset{H}{S} \;\; {}^{-}S-NR_3 \rightarrow R_3N: + HS-S-\overset{+}{N}R_3$

several steps

$HS-S_7-\overset{+}{N}R_3 \rightarrow H^+ + S^- \; S_6 \; S-\overset{+}{N}R_3 \rightarrow S_8 + :NR_3$

Equations 1 and 2 find analogy in Kice's mechanism for the acid hydrolysis of Bunte salts (12). The several steps of 4 represent the reversal of the reaction of S_8 with cyanide, phosphines, and other nucleophiles (13). Amine sulfides, postulated as unstable intermediates in step 3, have never yet been isolated; this contrast with the analogous amine oxides, which are comparatively stable, would indicate the great facility of steps 3-4.

Bunte salts are hydrolyzed by alkali to mixtures of sulfite ion, disulfides, sulfinates, and other products, possibly through the intermediacy of unstable sulfenic acids (5):

[5]


$$R\text{-}S\text{-}SO_3 + {}^{-}OH \longrightarrow R\text{-}S\text{-}OH + SO_3^{=}$$

[6] $$3\ R\text{-}S\text{-}OH \longrightarrow R\text{-}S\text{-}S\text{-}R + R\text{-}SO_2^{-} + H^{+} + H_2O$$

However, Tercinet reported that his compound $C_{21}H_{22}N_2O_5S_2$ from strychnine was converted by one equivalent of sodium hydroxide into "hydroxystrychnine", a compound for which no characteristics were reported. We have found that addition of one equivalent of sodium hydroxide to $C_{21}H_{22}N_2O_5S_2$ gave immediately a quantitative precipitation of strychnine, and not "hydroxystrychnine". The filtrate gave a positive test for sulfite ion. A possible mechanism for this reaction is:

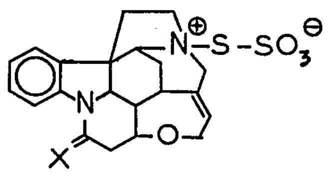
[7] $$R_3\overset{+}{N}\text{-}S\text{-}SO_3^{-} + OH^{-} \longrightarrow R_3\overset{+}{N}\text{-}S\text{-}OH + SO_3^{=}$$

[8] $$R_3\overset{+}{N}\text{-}S\text{-}OH + HO^{-} \longrightarrow R_3N + HO\text{-}S\text{-}OH$$

Equation 7 is analogous to equation 5, and equation 8 to the alkaline hydrolysis of an alkyl thioamine ($R_2N\text{-}S\text{-}NR_2$) to sulfoxylic acid ($S(OH)_2$) (14).

The facile recovery of strychnine by acid or alkaline treatment of Tercinet's product could be explained if the latter were merely the thiosulphate salt of strychnine ($C_{21}H_{24}N_2O_5S_2$). However, this possibility was excluded by preparation of the salt, which proved to be quite different. Treatment of an aqueous solution of the thiosulfate with sodium bicarbonate resulted in an immediate precipitation of strychnine, whereas Tercinet's product was unaffected under these conditions. Furthermore, molecular weight measurements (by vapor pressure osmometry) showed that the thiosulfate was dissociated into ions, whereas Tercinet's product had approximately the molecular weight expected for its formula $C_{21}H_{22}N_2O_5S_2$ (see Table V).

In summary, the evidence presented is best accommodated by the N-ammonium-S-thiosulfate zwitterion structure 3 (X=O) for the compound $C_{21}H_{22}N_2O_5S_2$ from strychnine, and by similar structures for analogous compounds obtained from brucine (1) and from dihydrostrychnine. Neostrychnine (pK_a 3.8:ref. 15) and pseudostrychnine (pK_a 5.6) did not react with sodium tetrathionate to give crystalline products. These amines are considerably less basic than strychnine, brucine, and dihydrostrychnine, all of which have $pK_a \simeq 7.4$



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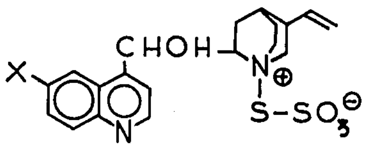

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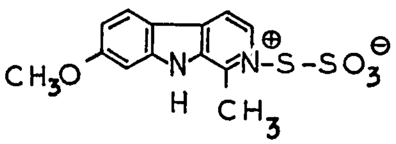

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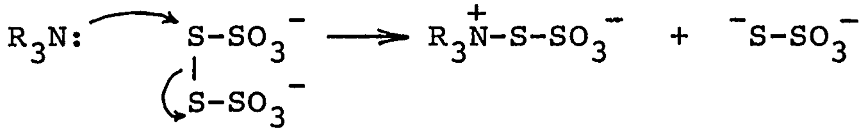
(15), and it seems likely that the N-ammonium-S-thiosulfate structure is formed by a reaction for which their amino

[9]



$$R_3N: \quad \begin{array}{l} S\text{-}SO_3^{-} \\ | \\ S\text{-}SO_3^{-} \end{array} \longrightarrow R_3\overset{+}{N}\text{-}S\text{-}SO_3^{-} \quad + \quad {}^{-}S\text{-}SO_3^{-}$$

centres are insufficiently nucleophilic[1]. Reaction 9 has parallels in the reaction of several other nucleophiles (eg., thiosulfate (16), cyanide (8c), azide (8c)) with tetrathionate ion.

On grounds of nucleophilicity, it might be expected that strychnidine would react at its more basic amino centre (15) with tetrathionate to give the compound 3 ($X=H_2$). This was confirmed by its ultraviolet spectrum (Table I), which was the same as that of strychnidine. Quaternization of the amino nitrogen joined to the aromatic ring would have resulted in a marked change of spectrum (17).

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[1] The steric congestion about the basic nitrogen atom of the strychnine bases may hinder reaction, and may furnish an additional reason for the failure of neostrychnine and of pseudostrychnine to react. It has been pointed out by a referee that neostrychnine and pseudostrychnine are stronger bases than the less hindered quinoline and 6-methoxyquinoline, which do react.

The question of reaction site also arises with respect to Tercinet's product $C_{20}H_{24}N_2O_5S_2$ from quinine and with the similar derivatives obtained from cinchonine and cinchonidine.[2] Again, these compounds are hydrolyzed by acid or alkali to the parent alkaloids, and so must have the thiosulfate group attached to nitrogen; this formulation is supported by molecular weight determinations, which exclude the possibility of thiosulfate salts. Attachment of $.S - SO_3^-$ to the more basic quinuclidine nitrogen, as shown in 4 (X=H or OMe) would be expected and is indicated by the ultra-violet spectra of these products, which are very similar to those of the parent alkaloids. Quaternization of the aromatic nitrogen would have caused significant shifts in the spectra, as shown by the spectrum of 6-methoxyquinoline hydrochloride recorded in Table I. In addition, the NMR spectra of the products are identical in the aromatic regions with the spectra of the parent compounds; quaternization of the aromatic nitrogen causes a downfield shift of peaks in this region, as shown in Table II for harmine, 6-methoxyquinoline and 2-phenyl[1,2-a]imidazopyridine.

The chemical reactions of the product obtained by Tercinet from harmine indicate again N-thiosulfonation. The NMR spectrum of the product (Table II) shows a deshielding

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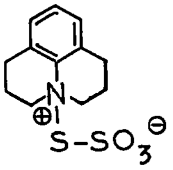
[2] Tercinet failed to obtain derivatives from cinchonine and cinchonidine, and hence concluded erroneously that the methoxyl group of quinine was necessary for reaction.

of the α- and β-protons of the pyridine portion of the molecule, similar to the deshielding in the trifluoroacetate salt. Furthermore, no N-H protons other than the original indole N-H proton were detected, indicating that the product was not a thiosulfate salt; this result was substantiated by vapor pressure osmometry, which showed that the compound $C_{13}H_{12}N_2O_4S_2$ was not dissociated. The ultraviolet spectrum of the product resembled very closely the spectrum of the hydrochloride of harmine (Table I). All of this diverse evidence supports the structure 5 for the product obtained by Tercinet from harmine, a structure expected from the fact that harmine quaternizes easily at the pyridine nitrogen (18).

If the Tercinet products are formed by the action of tetrathionate according to equation 9, it might be expected that products having the grouping $\geq\overset{+}{\mathrm{N}}\text{-S-SO}_3^{-}$ would be formed from other tertiary amines, but that quaternary ammonium ions would be unreactive. The latter supposition was supported by the failure of N-methylstrychninium chloride and of methylstrychnine (19) to react with tetrathionate. However, not all tertiary amines were found to react with sodium tetrathionate to give crystalline N-ammonium-S-thiosulfates. Amines giving crystalline products, and the structural formulae of the latter, are: julolidine, 6; quinoline, 7 (X=H); 6-methoxyquinoline, 7 ($X=OCH_3$); and 2-phenyl[1,2-a]imidazopyridine, 8. 3-Quinuclidinol gave a crystalline product in small yield for which no satisfactory analysis could be obtained. The structures shown are supported by the combustion analysis of the compounds, their molecular weights in ionizing solvents, and their ready hydrolysis in acid or alkali to regenerate the parent amine. The possibility of their being thiosulfate salts is excluded by their apparent molecular weights in solution and by their infrared spectra, recorded in Table III[3]. The structure 7 ($X=OCH_3$) for the product from 6-methoxyquinoline is in accord with its UV (Table I) and NMR (Table II) spectra, both of which indicate quaternization of the ring nitrogen.



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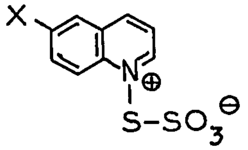

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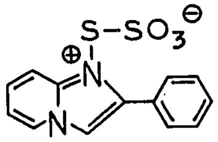

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Tertiary amines which failed to give any crystalline product with tetrathionate could be recovered after the reaction in high yield by extraction of the aqueous solution with ether. This suggests that the reaction represented by equation 9 is an equilibrium which does not always proceed far to the right, and that formation of N-ammonium-S-thiosulfate derivatives in good yields occurs only when the

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[3] Thiosulfates show significantly different spectra. Thus the thiosulfate of strychnine shows peaks (KBr) at 1150, 990, 750, and 550 cm^{-1}.

zwitterions have low solubility in the reaction medium and hence crystallize out during the reaction. In harmony with this idea, it was found that addition of increasing amounts of thiosulfate to the reaction mixture of strychnine and tetrathionate depressed the yield of 3 (X=O); however, it also caused the formation of sulfur in increasing amounts. The genesis of the sulfur is obscure; it does not come from the acid hydrolysis of 3 (X=O), because the pH of the solution remains near neutrality throughout the reaction. The depression of the yield of 3 (X=O) is probably due mainly to the mass-action effect of thiosulfate ion, a product of the reaction. However, it may be due partly to a destruction of tetrathionate from reaction with thiosulfate, since increasing amounts of sulfur were formed in the presence of increasing amounts of thiosulfate. Thiosulfate is known to catalyze the disproportionation of tetrathionate to trithionate and pentathionate (8c), and the latter can be imagined to decompose, by a series of steps analogous to those of equation 4, to give elemental sulfur and thiosulfate ion.

Compounds 3 (X=O), 4 ($X=OCH_3$), 7 ($X=OCH_3$ and 8 gave some protection to female mice (Swiss strain) against γ-radiation, but not enough to make them of interest as radioprotective agents.[5]

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[5] We are grateful to Dr. G.A. Grant, D.C.B.R.E., Shirley Bay, Ontario, for these tests.

EXPERIMENTAL

Infrared spectra were recorded with a Perkin-Elmer Model 337 spectrophotometer, nuclear magnetic resonance spectra with a Varian A-60 spectrophotometer, and ultraviolet spectra with a Unicam SP 800 spectrophotometer. Optical rotations were determined using a Carl Zeiss polarimeter, and molecular weights using a Mechrolab Model 301A osmometer. All melting points are uncorrected. Analyses were done by Dr. C. Daessle of Montreal and Dr. Alfred Bernhardt of Elbach über Engelskirchen, West Germany.

Materials

Strychnidine (20), dihydrostrychnine (21), and neostrychnine (22) were prepared by methods in the literature, and had the correct physical constants; the other alkaloids and bases were commercial products, and used without purification. Sodium tetrathionate was made according to Partington's method (23) by adding a saturated solution of sodium thiosulfate to a solution of iodine in alcohol at 10°. Potassium tetrathionate was obtained from K & K Rare Fine Chemicals.

Preparation of N-Ammonium-S-Thiosulfate Derivatives

(a) By a Modification of Tercinet's Method

Strychnine (1 g) and 12% sodium thiosulfate solution (80 ml) were heated on a steam bath with stirring. 10% silver nitrate solution (90 ml) was added slowly (20 min.). The mixture was heated for approximately 5 hours, by which time fumes of SO_2 and H_2S became evident. A black precipitate was deposited and a silver mirror formed on the walls of the flask. The reaction mixture was filtered hot. The filtrate on cooling deposited fluffy white crystals, which were washed with chloroform to remove unreacted strychnine, and recrystallized from ethanol to give white needles (1.23 g, 90% yield), m.p. 242-245° dec. (lit. 245° dec. (1)).

Brucine (70% yield), quinine (60%), cinchonine (15%), and harmine (50%) reacted by this method to give N-ammonium-S-thiosulfate products. However, strychnine methiodide, methyl betaine strychnine, benzyl strychnine, benzylstrychninium sulfate, 6-methoxyquinoline, isoquinoline, indole, 2-methylindole, and 1,2-dimethylindole did not give crystalline products, and could be recovered unchanged after the reaction by extraction with organic solvents or by crystallization from the reaction liquors.

(b) By Reaction with Sodium or Potassium Tetrathionate

Strychnine (1 g) and potassium tetrathionate (4 g) were heated on a steam bath in water (125 ml) for 2 hours; the mixture was then filtered hot. White crystals separated from the filtrate when cool, and were collected and washed with chloroform. They were recrystallized from ethanol to give pure N_b-strychninium-S-thiosulfate (1.3 g, 95%), m.p. 242-245° dec. Addition of a small amount of acetic acid reduced the reaction time to 1 1/2 hours, but the yield was only 75%. Excess acetic acid lowered the reaction time to 15 minutes, but the yield was only 30%.

Separate experiments showed that use of a smaller amount of tetrathionate, or of a shorter reaction time, led to lowered yields.

Compounds giving N-ammonium-S-thiosulfate derivatives and yields of the latter are shown in Table IV. 6-Methoxyquinoline, quinoline, and juolidine were used in the form of their sulfate salts, to solubilize them in the aqueous medium; the sulfate salt of strychnine also reacted to give the n-ammonium-S-thiosulfate. However, the following amines did not react: neostrychnine, pseudostrychnine, benzimidazole, imidazole, benzothiazole, pyridine, N-methylpiperidine, hexamethylenetetramine, 4-phenylpyridine, 2-anilinopyridine, tetrahydroisoquinoline, triethylamine, and triamylamine. 3-Quinuclidinol gave a crystalline compound (ν_{max}^{KBr} 1230, 1035, 690, 610 cm^{-1}) which had a bad combustion analysis.

Hydrolysis of N_b-Strychninium-S-thiosulfate in 6N Hydrochloric Acid

N_b-Strychninium-S-thiosulfate (2.63 g) was stirred at room temperature for a few minutes with 6N hydrochloric acid (50 ml). The yellow solution was extracted four times with chloroform to remove the color. The chloroform extracts when dried over magnesium sulfate and evaporated to dryness left a solid residue (0.18 g, 99%) which was identified as sulfur (no infrared absorption between 4000 and 400 cm^{-1}, UV absorption at 264 nm in ethanol (log ε 3.0) with a shoulder at 275 nm (16)). Barium chloride (few mls of 10% solution) was added to the aqueous layer. Barium sulfate precipitated, was removed by filtration and dried to constant weight (1.30 g, 98.5%). The aqueous layer was neutralized with sodium bicarbonate. A white precipitate (1.877 g, 99.3%) separated which was identified as strychnine, m.p. 285-288° dec. (lit. 286-288° dec.), by an IR spectrum identical to that of an authentic sample of strychnine.

Hydrolysis of N_b-Strychninium-S-thiosulfate in Sodium Hydroxide

N_b-Strychninium-S-thiosulfate (1.57 g, 3.537 meq.) was exactly neutralized by addition of sodium hydroxide (22.15 ml, 0.1597 N, 3.535 meq.). A white precipitate of strychnine (1.18 g, 3.533 meq., m.p. 286-288° dec.) identified by IR spectrum, was formed during the titration. The aqueous solution gave a positive test for sulfite (a precipitate with barium chloride that was soluble in acid; iodine was decolorized by the solution). No sulfur could be detected.

The same hydrolysis took place with aqueous ammonia or sodium carbonate, but not with sodium bicarbonate. The compound was somewhat soluble in warm bicarbonate solution, but could be recovered unchanged on cooling. An aqueous solution of the thiosulfate salt of strychnine, prepared by mixing warming aqueous solutions of the hydrochloride of the alkaloid and of sodium thiosulfate and filtering off the precipitate, gave strychnine immediately on treatment with sodium bicarbonate.

Reaction of Strychnine with Sodium Tetrathionate in the Presence of Sodium Thiosulfate

Strychnine (0.50 g) and sodium tetrathionate (1.66 g) in water (50 ml) were heated on a steam bath at 100° for 2 hours. The solution was cooled to 0°, and the crystals that formed were collected. The crystals were extracted with chloroform, leaving a residue of zwitterion 3 (X=O) (580 mg, 87%). The chloroform extract was dried over magnesium sulfate, and evaporated. The residue (140 mg) from the chloroform extract was boiled in water (100 ml) to dissolve a small amount of strychnine, leaving insoluble sulfur (75 mg), identified as above. The aqueous extract was evaporated to give strychnine (65 mg, 13%).

A similar reaction with 0.585 g of sodium thiosulfate added gave 3 (X=O) (386 mg, 57.5%), strychnine (204 mg, 40.5%), and sulfur (185 mg). When the amount of thiosulfate was increased to 2.51 g, the yields were: 3 (X=O) (203 mg, 30%), strychnine (355 mg, 67%), and sulfur (310 mg).

In separate experiments it was shown that in water at 100° the solubility of strychnine was 7.9×10^{-4} M, and of 3 (X=O), 1.5×10^{-2} M, so that both compounds were present in the first experiment above in amounts greater than required for saturation.

ACKNOWLEDGMENTS

We acknowledge gratefully the financial support of Abbott Laboratories and of the National Research Council. We are indebted to Mr. Anwer Mehkeri for bringing the problem to our attention, and for a preliminary experiment.

TABLE I

Ultraviolet Spectra in Ethanolic

Compound	$\lambda\lambda_{\mathrm{ma}}$
Strychnine	254(17800),
<u>3</u>, X = O	254(17800),
Strychnidine	254(17700),
<u>3</u>, X = H_2	254(17700),
Brucine	254(17800),
N_b-Brucinium-S-thiosulfate	254(17800),
Quinine	232(74400),
<u>4</u>, X = OCH_3	232(74400),
Cinchonine	227(47000),
<u>4</u>, X = H	227(47000),
Harmine	242(24100),
Harmine hydrochloride	249(18000),
<u>5</u>	249(18000),

ABLE I

ra in Ethanolic Solution

$\lambda\lambda_{max}$(nm) and $\varepsilon\varepsilon$*		
254(17800),	280(6100),	288(4810)
254(17800),	280(6100),	288(4800)
254(17700),	303(2500),	
254(17700),	303(2500),	
254(17800),	280(6100),	288(4800)
254(17800),	280(6100),	288(4800)
232(74400),	279(8740),	332(11100)
232(74400),	279(8750),	332(11100)
227(47000),	284(7790),	314(4850)
227(47000),	284(7790),	314(4860)
242(24100),	307(10200),	
249(18000),	325(10600),	
249(18000),	325(10600),	

TABLE I cont . . .

Compound	λ
6-Methyoxyquinoline	229(27000),
6-Methyoxyquinoline hydrochloride	250(27700),
7, X = OCH_3	250(27700),
2-Phenyl[1,2-a]imidazopyridine	245(34500),
2.Phenyl[1,2-a]imidazopyridine hydrochloride	239(20700),
8	239(20700),

* in parentheses.

I cont . . .

$\lambda\lambda_{max}$(nm) and $\varepsilon\varepsilon$*		
229(27000),	269(2830),	327(4000)
250(27700),	312(4100),	340(4100)
250(27700),	312(4100),	340(4100)
245(34500),	322(8830),	
239(20700),	303(15200)	
239(20700),	303(15200)	

TABLE II

Selected Nuclear Magnetic R

Compound	
Cinchonine	4
4, X = H	4
Quinine	4
Harmine	4
Harmine trifluoroacetate salt	4
<u>5</u>	4
6-Methyoxyquinoline ≠	4
6-Methoxyquinoline trifluoroacetate salt	4
<u>7</u>, X = OCH_3	4
2-Phenyl[1,2-a]imidazopyridine	4
2-Phenyl[1,2-a]imidazopyridine trifloroacetate salt	5
<u>8</u>	5

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*Resonances in H_z downfield from tetrameth
solvent, dimethylsulfoxide - d_6, except

§Aromatic protons
¶Indole NH
‖ Protons at 2-position

TABLE II

lear Magnetic Resonance Data

	Resonances*
	456 - 534 (m, 6H)
	456 - 534 (m, 6H)
	464 - 546 (m, 5H)
	462 - 494 (m, 2H) , 680 (s, 1H)
lt	475 - 500 (m, 2H) , 740 (s, 1H)
	475 - 500 (m. 2H) , 740 (s, 1H)
	418 - 520 (m, 5H) , 522 (d, 1H)[11]
oacetate	445 - 550 (m, 5H) , 547 (d, 1H)[11]
	445 - 550 (m, 5H) , 547 (d, 1H)[11]
line	499 (s, 1H), 508 (d, 1H)
line	514 (s, 1H), 527 (d, 1H)
	514 (s, 1H), 527 (d, 1H)

l from tetramethylsilane in a 60 MH_z instrument;
- d_6, except ≠ $CDCl_3$

TABLE II

ses of N-ammonium sulfonates

	%C	%H	%N	%S	mol. wt.[*]
alc.	60.9	5.3	6.8	7.7	414
ound	60.6	5.5	6.8	7.5	410 ± 10(EtOH)
alc.	58.2	5.5	5.9	8.7	
ound	58.4	5.6	5.8	8.7	
alc.	60.9	5.9	7.5	8.5	
ound	60.7	6.1	7.5	8.5	
alc.	59.4	6.0	6.9	7.9	
ound	59.1	5.9	7.2	8.2	
alc.	53.4	4.1	9.6	10.9	
ound	53.5	4.4	9.4	11.0	
alc.	50.2	3.8	5.9	13.4	239
ound	50.0	3.7	5.8	13.4	235 ± 10(EtOH)
alc.	56.9	3.7	10.2	11.7	274
ound	56.7	3.5	9.9	11.5	270 ± 10(EtOH)

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etry using a Mechrolab Model 301A osmometer and the

TABLE III

Infrared peaks (cms^{-1}) of

N-ammonium-S-thiosulfate derivative in KBr.

Parent amine	$\nu_{asym}(SO_3)$	$\nu_{sym}(SO_3)$	ν(s-N)	$\delta(SO_3)$
Strychnine	1250	1020	705	610
Brucine	1250	1020	705	610
Harmine	1240	1020	732	610
Quinine	1250	1020	705	615
Cinchonine	1250	1015	705	610
Cinchonidine	1150	1015	690	610
Strychnidine	1250	1015	705	610
Dihydrostrychnine	1250	1020	705	610
6-Methoxyquinoline	1250	1020	755	615
Quinoline	1240	1020	760	610
Juolidine	1260	1010	725	600
2-Phenyl[1,2-a] imidazopyridine	1250	1012	750	600

TABLE IV

Physical Properties of N-ammonium-S-thiosulfates

Parent amine	M.P.°C*	Yield%
Strychnine	242-245° **	90
Brucine	192-195 +	90
Harmine	170-175 ≠	75
Quinine	187-189 §	85
Cinchonine	180-185	50
Cinchonidine	192-195	50
6-Methoxyquinoline	185-187	60
Quinoline	255-260	20
Juolidine	178-180	50-60
2-Phenyl[1,2-a] imidazopyridine	205-210	80-85
Strychnidine	235-240	40-50
Dihydrostrychnine	290-295	75

* All melting points involved decomposition of sample.

** Found: $[\alpha]_D$ -52.5° (EtOH); reported, -50° (1)

\+ Found: $[\alpha]_D$ -66° (H_2O; reported, -64° (1)

≠ Found: $[\alpha]_D$ +19.7° (EtOH); reported +19.5° (1)

§ Found: $[\alpha]_D$ -155° (EtOH); reported, -151.7° (1)

TABLE V

Analyses of N-ammonium-S-thio

Parent amine	Product empirical formula		%C	%H	%N
Strychnine;	$C_{21}H_{22}N_2O_5S_2$	calc.	56.48	4.96	6.27
		found	56.41	4.90	6.31
Brucine;	$C_{23}H_{26}N_2O_7S_2$	calc.	54.75	5.19	5.55
		found	55.00	5.28	5.43
Harmine;	$C_{13}H_{12}N_2O_4S_2$	calc.	48.14	3.76	8.64
		found	48.33	3.86	8.88
Quinine;	$C_{19}H_{24}N_2O_5S_2$	calc.	55.03	5.54	6.42
		found	55.05	5.52	6.32
Cinchonine;	$C_{18}H_{22}N_2O_4S_2$	calc.	56.14	5.45	6.89
		found	56.30	5.36	6.93
Cinchonidine;	$C_{18}H_{22}N_2O_4S_2$	calc.	56.14	5.45	6.89
		found	56.25	5.57	6.78
6-Methoxy-quinoline	$C_{10}H_9NO_4S_2$	calc.	44.29	3.35	5.17
		found	44.39	3.60	5.31

TABLE V

N-ammonium-S-thiosulfates

%C	%H	%N	%S	Mol. Wt.*
56.48	4.96	6.27	14.36	446.5
56.41	4.90	6.31	14.45	440±O (EtOH, H_2O, MeOH)
54.75	5.19	5.55	12.71	504.5
55.00	5.28	5.43	12.81	505±10 (EtOH)
48.14	3.76	8.64	19.77	324.3
48.33	3.86	8.88	20.01	320±10 (MeOH)
55.03	5.54	6.42	14.69	436.5
55.05	5.52	6.32	14.48	425±10
56.14	5.45	6.89	15.76	406.5
56.30	5.36	6.93	15.83	395±10 (MeOH)
56.14	5.45	6.89	15.76	406.5
56.25	5.57	6.78	15.90	
4.29	3.35	5.17	23.60	271.1
4.39	3.60	5.31	23.34	270±10 (H_2O)

TABLE V cont . .

Parent amine	Product empirical formula		%C	%H	%N
Quinoline;	$C_9H_7NO_3S$	calc.	44.82	2.93	5.8
		found	44.70	2.95	5.6
Juolidine;	$C_{12}H_5NO_3S$	calc.	50.52	5.30	4.9
		found	50.39	5.28	4.7
2-phenyl[1,2-a]	$C_{12}H_{10}N_2O_3S$	calc.	50.98	3.29	9.1
		found	50.69	3.57	8.9
Strychnidine;	$C_{21}H_{24}N_2O_4S_2$	calc.	55.99	5.82	6.2
		found	55.89	5.67	6.4
Dihydrostrychnine	$C_{21}H_{24}N_2O_5S_2$	calc.	56.24	5.39	6.2
		found	56.29	5.41	6.5

* by vapor pressure osmometry in the solvents indica

E V cont . . .

C	%H	%N	%S	Mol. Wt.*	
32	2.93	5.81	26.54	241.1	
70	2.95	5.69	26.64	240±10	(MeOH)
52	5.30	4.91	22.43	285.2	
39	5.28	4.77	22.56	285±10	(H_2O)
98	3.29	9.15	20.89	306.2	
59	3.57	8.93	20.64	300±10	(EtOH)
99	5.82	6.22	14.20	432.4	
39	5.67	6.48	14.38		
24	5.39	6.25	14.28	448.5	
29	5.41	6.50	14.49		

lvents indicated.

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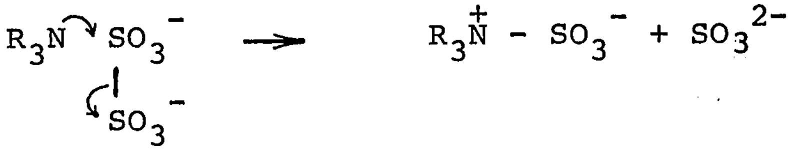
CHAPTER 2

THE REACTION OF TERTIARY AMINES WITH SODIUM DITHIONATE

Tertiary amines react with sodium dithionate in boiling water to give the amine-sulfur trioxide complexes (substituted sulfamic acids).

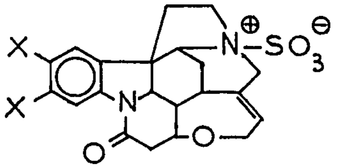
Les amines tertiares fournissent avec le dithionate de soude en eau bouillante les complexes d'amines avec le trioxide de soufre.

While there are many examples of nucleophilic displacement on a sulfur atom of the higher polythionates (1,2), there have been few if any involving dithionate. (A possible example might be the acid-catalyzed hydrolysis of dithionate (3)). We have now found that many (but not all) tertiary amines react with dithionate in boiling water to form the amine-sulfur trioxide complexes (which can be regarded as substituted sulfamic acids[1]):



$$R_3N + {}^{-}O_3S{-}SO_3^{-} \longrightarrow R_3\overset{+}{N} - SO_3^{-} + SO_3^{2-}$$

The utility of the reaction was demonstrated by preparing the derivatives 1 (X=H) from strychnine, 1 (X=OMe) from brucine, 2 (X=H) from cinchonine, 2 (X=OMe) from quinine, 3 from harmine, 4 from 6-methoxyquinoline, and 5 from 2-phenyl-[1,2-a]imidazopyridine.



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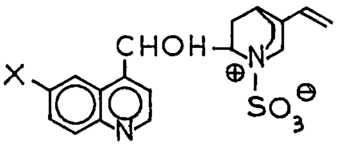

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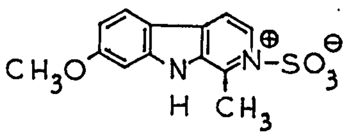

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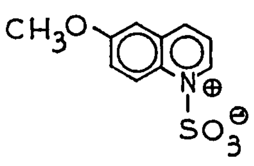

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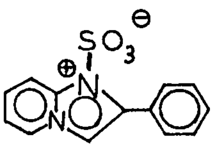

5

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[1] Sulfamic acid has the zwitterionic structure $^{+}H_3N - SO_3^{-}$ (4).

Their sulfamic acid structures were demonstrated by preparing them also by reaction of the amines with pyridine-sulfur trioxide complex (used for 1 (X=H and OMe), 2 (X=H and OMe), and 3), or with sulfur trioxide in 1,2-dichloroethane or chlorosulfonic acid in chloroform (used for 4 and 5). The structures 2 (X=H or OMe) for the products from cinchonine or quinine, expected on general grounds to be preferred over the alternative structures having sulfur trioxide complexed to the quinoline nitrogen (1), were supported by the ultraviolet absorption and nuclear magnetic resonance characteristics of the compounds (see Experimental and discussion in ref. 1). The structure 3 for the product from harmine was supported by similar evidence, while the structure 5 for the product from 2-phenyl[1,2-a]imidazopyridine seemed most plausible because it allowed maximum delocalization of the positive charge.

All of the sulfamic acid derivatives are new compounds, with the exception of 1 (X=H and OMe), which have been obtained previously (5) by routes which left their structures in doubt; these are discussed elsewhere (6). The sulfamic acids are fairly stable in water, but are rapidly hydrolysed in dilute acid or alkali to the parent amine and sulfate ion.

EXPERIMENTAL

Preparation of amine-sulfur trioxide complexes

(a) By reaction of the amine with sulfur trioxide

A mixture of strychnine (0.5 g), dissolved in dry pyridine (40 ml), and pyridine-sulfur trioxide complex (0.24 g) was stirred for 15 mins. at room temperature. A white solid separated, which was removed by filtration, washed with pyridine, and dried under reduced pressure at room temperature. The solid 1 (X=H) (0.5 g) melted at 265-275°C(dec.) (Osterlin (5) reported m.p. 260-265° C), ν_{max}^{KBr} 1250, 1000, 700, 575 cm^{-1}.

By essentially the same procedure the complex 1 (X=OMe) was obtained from brucine, 2 (X=OMe) from quinine, 2 (X=H) from cinchonine, and 3 from harmine. The complexes 4 and 5 were obtained by the reaction of the parent amines with equivalent amounts of sulfur trioxide dissolved in 1,2-dichloroethane at 0° (cf. ref. 7) or by reaction of the parent amines with half-molar quantities of chlorosulfonic acid in chloroform at 0° (cf. ref. 8). The physical properties of these compounds are listed in Table I and their combustion analyses in Table II. The ultraviolet absorption and nuclear magnetic resonance spectra of these compounds were obtained, and did not differ essentially from the spectra of the analogous N-ammonium-S-thiosulfate compounds already reported (1).

(b) By reaction of the amine with dithionate

A suspension of strychnine (1 g) in a solution of sodium dithionate (4 g) in water (90 ml) was refluxed for 5 hours. The hot reaction mixture was filtered to remove unreacted strychnine and cooled. White crystals separated and were removed, washed with water and chloroform, and recrystallized from water or ethanol. The solid thus obtained

(1.1 g, 95%), m.p. 265-275° (dec.), had an infrared spectrum identical with that of material prepared above.

By essentially the same procedure, the following sulfamic acids were obtained from the free bases in the yields indicated: 1 (X=OMe), 83%; 2 (X=OMe), 80%; 2 (X=H), 95%; 3, 80%; 4, 60%; 5, 96%.

The following amines failed to give any crystalline product after reaction with dithionate: triethylamine, N,N-dimethylaniline, imidazole, benzimidazole, 4-phenylpyridine, benzothiazole, and neostrychnine.

ACKNOWLEDGMENT

Financial support from the Abbott Laboratories and from the National Research Council is gratefully acknowledged.

TABLE I

Melting points and infrared peaks (cm^{-1}) in KI

Compound	M.p. (°C)*	$\nu_{asym}(SO_3)$	ν
1; X = H	265-275°	1250	
1; X = OMe	238-240°	1225	
2; X = H	230-233°	1240	
2; X = OMe	210-215°	1245	
3	220-225°	1230	
4	183-185°	1250	
5	208-210°	1225	

*All melting points involved decomposition of the sam

TABLE I

s (cm^{-1}) in KBr of N-ammonium sulfonates

$_{\text{ym}}(\text{SO}_3)$	$\nu_{\text{sym}}(\text{SO}_3)$	$\nu(\text{S-N})$	$\delta(\text{SO}_3)$
250	1000	700	575
225	990	710	580
240	990	720	575
245	990	720	575
230	1010	730	570
250	1015	755	590
225	990	755	570

ion of the sample.

TABLE II

Analyses of N-ammonium s

Compound	Empirical Formula		%C	%H
1; X = H	$C_{21}H_{22}N_2O_5S$	calc.	60.9	5.
		found	60.6	5.
1; X = OMe	$C_{23}H_{26}N_2O_7S$	calc.	58.2	5.
		found	58.4	5.
2; X = H	$C_{18}H_{22}N_2O_4S$	calc.	60.9	5.
		found	60.7	6.
2; X = OMe	$C_{19}H_{24}N_2O_5S$	calc.	59.4	6.
		found	59.1	5.
3	$C_{13}H_{12}N_2O_4S$	calc.	53.4	4.
		found	53.5	4.
4	$C_{10}H_9NO_4S$	calc.	50.2	3.
		found	50.0	3.
5	$C_{12}H_{10}N_2O_3S$	calc.	56.9	3.
		found	56.7	3.

---

*Determined by vapour phase osmometry using a Mechr
solvent indicated.

TABLE II

of N-ammonium sulfonates

	%C	%H	%N	%S	mol. wt.*
c.	60.9	5.3	6.8	7.7	414
nd	60.6	5.5	6.8	7.5	410 ± 10(EtOH)
c.	58.2	5.5	5.9	8.7	
nd	58.4	5.6	5.8	8.7	
c.	60.9	5.9	7.5	8.5	
nd	60.7	6.1	7.5	8.5	
c.	59.4	6.0	6.9	7.9	
nd	59.1	5.9	7.2	8.2	
c.	53.4	4.1	9.6	10.9	
nd	53.5	4.4	9.4	11.0	
c.	50.2	3.8	5.9	13.4	239
nd	50.0	3.7	5.8	13.4	235 ± 10(EtOH)
c.	56.9	3.7	10.2	11.7	274
nd	56.7	3.5	9.9	11.5	270 ± 10(EtOH)

cy using a Mechrolab Model 301A osmometer and the

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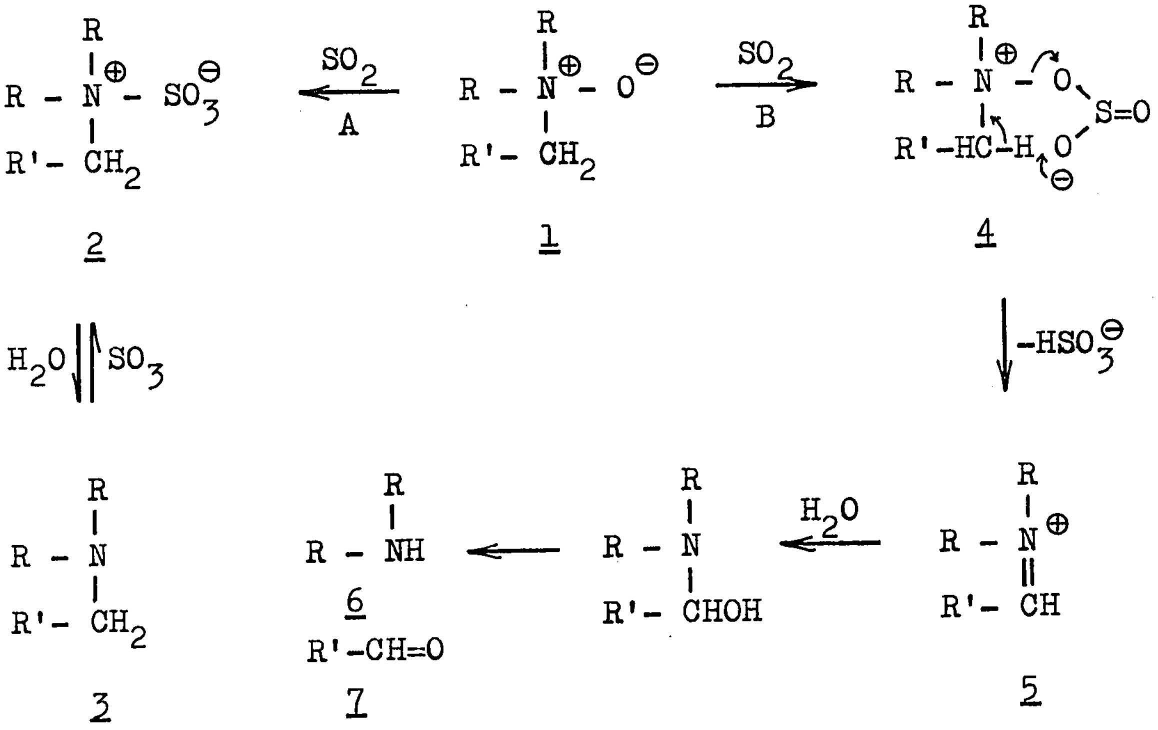
CHAPTER 3

REACTION OF AMINE OXIDES WITH SULFUR DIOXIDE

Strychnine N-oxide (14; X=H) reacts with sulfur dioxide in benzene to form the sulfitoamine 15 (X=H), which rearranges rapidly in boiling water to the substituted sulfamic acid 16 (X=H) by a free-radical mechanism. The sulfamic acid 16 (X=H) is formed by reaction of amine oxide with cold aqueous sulfur dioxide, and may be an intermediate in the reduction of the amine oxide by sulfur dioxide in hot water. With aqueous sulfur dioxide at 0°, N,N-dimethylbenzylamine N-oxide gives tertiary amine by reduction and secondary amine and aldehyde by a Polonovski-type reaction; however, N,N-dimethylaniline N-oxide gives tertiary amine, o- and p-dimethylaminobenzene sulfonic acids, but no appreciable amount of secondary amine. The sulfonic acids are probably formed by a free-radical mechanism, since their formation is largely suppressed by the addition of hydroquinone. N,N-Diethylaniline N-oxide gives similar products.

La réaction de l'oxide de strychnine (14; X=H) avec la dioxide de soufre en benzene fournit le compose 15 (X=H). En eau bouillante celle-ci réarrange a l'acide sulfamique 16 (X=H) par un mécanisme radicalaire. L'acide sulfamique est probablement l'intermediare quand l'oxide est réduit par la dioxide de soufre dans l'eau chaude. La dioxide de soufre reagit avec l'oxide de N,N-dimethylbenzylamine à 0° pour fournir en partie l'amine tertiare, et en partie aldehyde et une amine secondaire; avec l'oxide de N,N-dimethylaniline elle fournit en partie l'amine tertiare, en partie les acides o- et p-dimethylaminobenzene sulfoniques, mais rien d'amine secondaire. Les acides sulfoniques sont probablement formées par un méchanisme radicalaire, parce qu'on peut les supprimer par l'addition de hydroquinone à la réaction. L'oxide de N,N-diethylaniline fournit des produits semblables.

The reaction of an amine oxide (1)with aqueous sulfur dioxide can take two routes (A and B in Scheme 1). The most commonly observed route (A) has been that leading to a tertiary amine (3) (1-3) and sulfate ion, and it has been assumed that these products come from the hydrolysis of an intermediate sulfamic acid[1] derivative 2 (1). No mechanism has been advanced for the reaction 1→2, in which an N-O bond becomes replaced by an N-S bond. However, the reaction of sulfur dioxide with an amine oxide has sometimes been found to lead to a secondary amine and an aldehyde (route B), a reaction that is reminiscent of the Polonvski reaction (5). Thus Lecher and Hardy, from the reaction of trimethylamine



SCHEME 1

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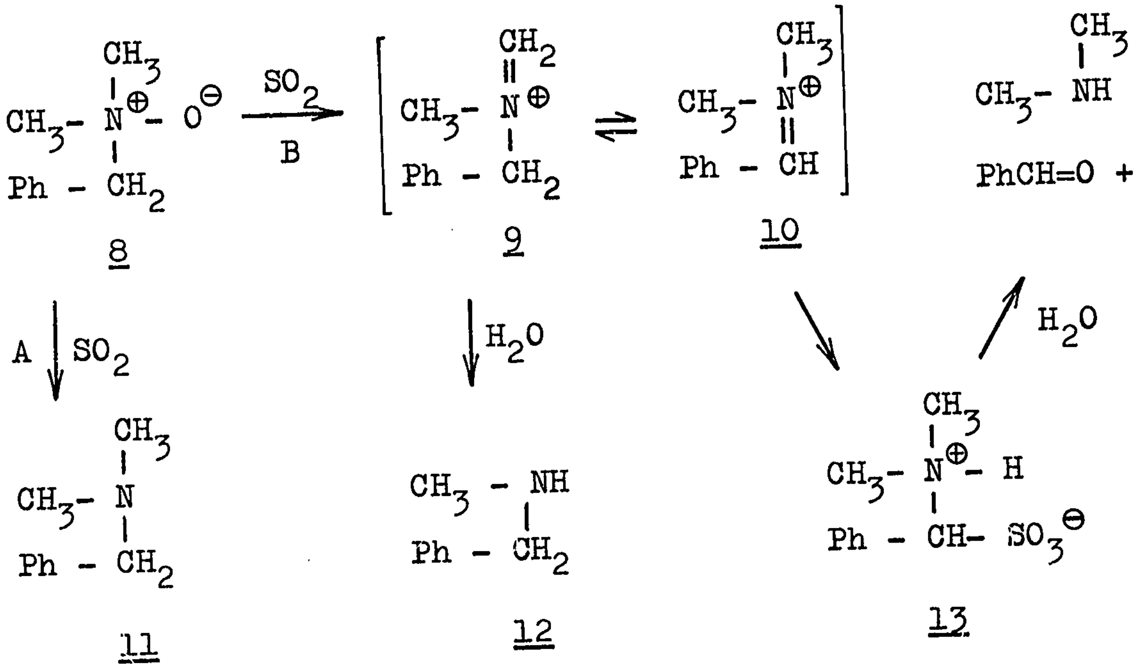
[1] Sulfamic acid has the zwitterionic structures $H_3N^{\oplus}-SO_3^{\ominus}$ (4).

oxide (1; R=Me, R'=H) obtained only 15-20% of trimethylamine (3; R=Me, R'=H) and less than 5% of the sulfamic acid 2 (R=Me, R'=H), the route A products, and more than 50% of dimethylamine (6; R=Me) and formaldehyde (7; R'=H), the route B products (6). The mechanism which has been suggested for route B (7) is shown in Scheme 1. Wiewiorowski and Baranowski (7) found that reaction of sparteine N_{16}-oxide and lupanine N-oxide with aqueous sulfur dioxide went about 20% by route A and 80% by route B; however, reaction of α-isosparteine N-oxide and sparteine N_1-oxide went 100% by route A. In the latter two cases the ring systems are such that the unsaturated intermediate 5 would be considerably strained; the Polish authors suggested that for this reason route B was avoided and route A followed exclusively.

We have now found that reaction of N,N-dimethylbenzylamine oxide (8) with aqueous sulfur dioxide also follows both routes, as shown in Scheme 2. A 35% yield of tertiary amine 11 (route A) and 8% yield of secondary amine 12 (route B) was obtained, as well as a 52% yield of the aminosulfonic acid 13 (route B). The structure of the latter was evident from its analysis, infrared spectrum, and the fact that on attempted recrystallization from water or 95% ethanol it decomposed to benzaldehyde (and presumably dimethylamine and sulfurous acid). The effect of the phenyl group would be expected to favour the formation of the unsaturated intermediate 10 over 9, as was observed.

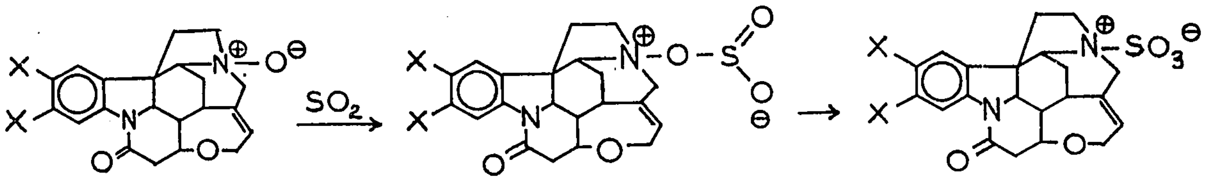
In order to study the mechanism of route A, the



SCHEME 2

reaction of strychnine N-oxide (14; X=H) was investigated. Because of the bridgehead position of the quaternary nitrogen atom, little or no reaction by route B should be expected, and in fact none was observed. The reaction of strychnine N-oxide with sulfur dioxide in hot water (exact temperature unspecified) was first reported by Pictet and Mattison (8), who obtained strychnine and sulfate ion. However, Polonovski and Polonovski (9) and Leuchs and Rack (10) showed that a sulfamic acid 16 (X=H), reported m.p.>330°, was also formed. The sulfamic acid was readily hydrolysed in hot aqueous sodium carbonate to strychnine and sulfate ion. Oesterlin (11) claimed to obtain exclusively a sulfamic acid 16 (X=H), m.p. 260-265°, from the reaction of strychnine N-oxide with sodium bisulfite in cold methanol, but exclusively strychnine and sulfate ion from its reaction with sodium bisulfite in water at 60°.

We have confirmed that the course of the reaction depends upon temperature, since we found that strychnine N-oxide reacts with an excess of sulfur dioxide in water at 60-65° to give strychnine (95% yield) but at 0° to give the sulfamic acid 16 (X=H), m.p. 265-275° (85% yield). The sulfamic acid structure for this compound has been established by synthesizing it also by reaction of strychnine with pyridine-sulfur trioxide complex (a reaction of the type 3 → 2) (12). The compound 16 (X=H) was fairly stable in hot water, but was rapidly hydrolyzed in dilute acid or alkali to strychnine and sulfate ion, even the very weakly acidic solution of sulfur dioxide in water at 65° was sufficient for rapid hydrolysis. It is consequently a possible (though not a necessary) intermediate in the formation of the amine from the amine oxide, but one is still left with the question: how does the N-O bond of the amine oxide 14 become converted into the N-S bond of the sulfamic acid 16?



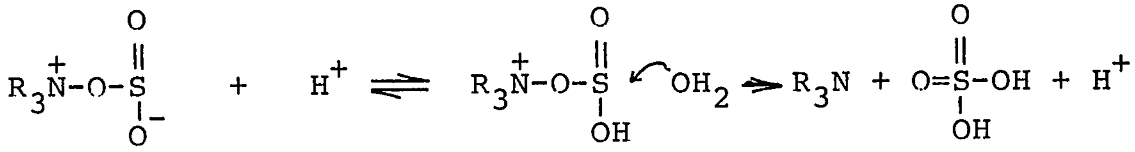
14 15 16

A possible intermediate in this transformation is the sulfitoamine 15 (X=H), which we have isolated from the reaction of the amine oxide with sulfur dioxide in benzene.

Analogously, from brucine N-oxide we obtained 15 (X=OMe). Previously, Lecher and Hardy (6) had obtained by a similar reaction the sulfitoamine 4 (R-Me, R$'$=H) from trimethylamine N-oxide. However, while in cold water Lecher and Hardy's compound underwent a Polonovski-type reaction to give dimethylamine (7;R=Me) and formaldehyde (8; R$'$=H), the compound 15 (X=H) was unchanged in cold water. In boiling water it was isomerized into 16 (X=H), but in aqueous acid or alkali it was hydrolyzed to strychnine and sulfate ion:

[1] 

$$R_3\overset{+}{N}-O-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{S}}\ \ OH^- \longrightarrow R_3N + O=\overset{\overset{O}{\|}}{\underset{\underset{O}{|}}{\overset{-}{S}}}-OH$$

[2] 

$$R_3\overset{+}{N}-O-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{S}} + H^+ \rightleftharpoons R_3\overset{+}{N}-O-\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{S}}\ \ OH_2 \longrightarrow R_3N + O=\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{S}}-OH + H^+$$

Even the weakly acidic solution of sulfur dioxide in water was able to effect complete hydrolysis of 15 (X=H) to strychnine within 15-20 minutes at 65-70°. Thus in the case of strychnine N-oxide, either the sulfitoamine 15 (X=H) or the sulfamic acid 16 (X=H) may be involved as intermediates in the reduction to the tertiary amine.

After the rearrangement of 15 (X=H) into 16 (X=H) in water at 100°, no sulfate ion can be detected in the solution, so that it is unlikely that the isomerization proceeds by the route:

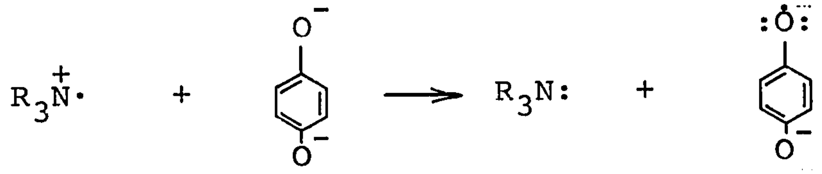
[3] $R_3\overset{+}{N}-O-SO_2^- \longrightarrow R_3N + SO_3 \longrightarrow R_3\overset{+}{N}-SO_3^-$

(a route, furthermore, which would be disfavoured by a polar solvent (13)). A more plausible route involves dissociation of the sulfitoamine into ion-radicals (14):

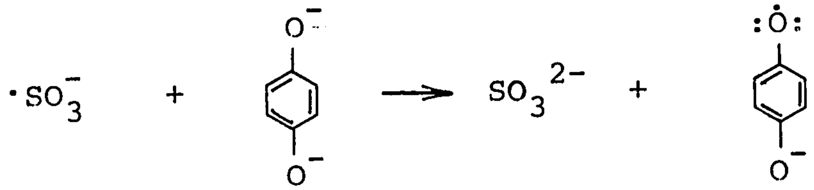
$$[4] \qquad R_3\overset{+}{N}\text{-O-}SO_2^- \longrightarrow R_3\overset{+}{N}\cdot + \cdot SO_3^- \longrightarrow R_3\overset{+}{N}\text{-}SO_3^-$$

This mechanism receives support from the observation that in boiling water in the presence of the radical trap hydroquinone (14) only 25% of <u>15</u> (X=H) is isomerized to <u>16</u> (X=H), and 60% is reduced to strychnine and sulfite ion.

[5]



[6]



The rearrangement of <u>15</u> (X=H) into <u>16</u> (X=H) proceeds too slowly to account for the formation of <u>16</u> (X=H) (85% yield in 15 minutes) from the reaction of strychnine N-oxide with aqueous sulfur dioxide at 0°; even at 100°, rearrangement of <u>15</u> (X=H) into <u>16</u> (X=H) is only about 50% complete in 15 minutes. However, it is possible that <u>16</u> (X=H) is formed by the union of two radical ions produced directly by a reaction of the type:

$$[7] \qquad R_3\overset{+}{N}\text{-OH} + SO_3^{2-} \longrightarrow R_3\overset{+}{N}\cdot + OH^- + \cdot SO_3^- \longrightarrow R_3\overset{+}{N}\text{-}SO_3^-$$

Such a one-electron oxidation-reduction finds analogy in the reduction of amine oxides to aminium radical-ions by the one-electron reducing agent, iron (II) (15). Support for the mechanism of equation [7] comes from the observation that the formation of the sulfamic acid 16 (X=H) can be suppressed completely when strychnine N-oxide reacts with sulfur dioxide in water at 0° in the presence of hydroquinone.[2]

The change in the course of the reaction when the solvent is changed from benzene to water probably depends on a change in the nature of the reactants: the amine oxide is protonated in weak aqueous acids (16), and the sulfur dioxide is converted in part into the strongly-reducing sulfite ion.

Further evidence for reactions [4] and/or [7] came from a study of the reaction of N,N-dimethylaniline oxide with sulfur dioxide (Scheme 3). In benzene the unstable sulfitoamine 18 was formed; however, in water this decomposed to give no appreciable quantities of route B products (as

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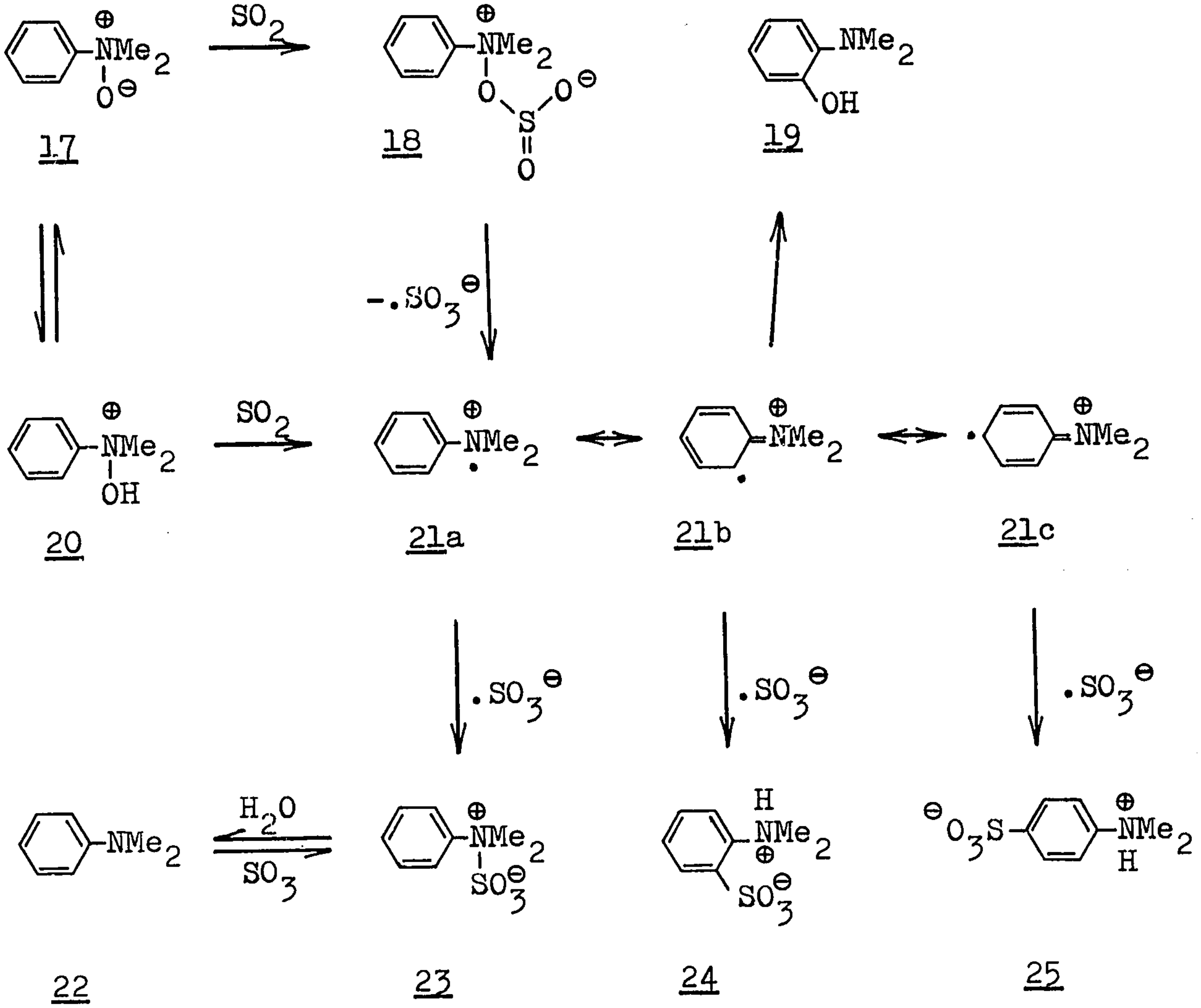
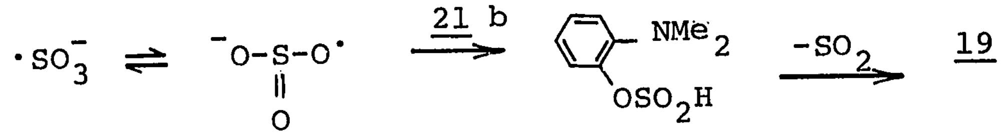
[2] Hydroquinone had no effect on the course of the reaction of N,N-dimethylbenzylamine N-oxide with aqueous sulfur dioxide, under the conditions described in the Experimental Section, so that free radical intermediates are probably not involved in the reactions of route B.



SCHEME 3

might have been expected from the close structural similarity between 17 and 8), but only the products to be expected from our mechanism (equation [4]) for route A . These products are shown in Scheme 3, and their yields are given in Table I. Besides the tertiary amine 22, the *ortho*- (24) and *para*-sulfonic (25) acids were obtained along with a trace of the o-aminophenol 19. The latter may have come *via* an unstable sulfite ester:

[8]



None of the sulfamic acid zwitterion 23 was isolated, because even at 0° this compound (unlike corresponding aliphatic zwitterions such as 16) is extremely readily hydrolyzed by water alone.

The predominance of route A products from the reaction of this amine oxide is explained by the resonance stabilization of the aminium ion 21, which makes homolytic fission according to reaction [4] much more facile than the competing reaction 4 → 5 of route B. The facilitation of reaction [4] is further shown by the fact that the sulfitoamine 18 underwent reaction in water at 0° within a few hours, during which time the sulfitoamine 15 had not reacted completely in water even at 100°.

About the same yields of products 19, 22, 24, and 25 were obtained by treating the amine oxide 19 with sulfur dioxide in water at 0° (a reaction studied by Bamberger (17) more than seventy years ago), as shown in Table I. This may indicate that Bamberger's reaction also involves the sulfitoamine 18 as an intermediate, although the alternative pathway (17→20→21→products), based on equation [7], cannot be excluded at the moment. Either pathway involves the intermediary of the aminium ion 21; this accords with the observation that in the presence of a radical scavenger, hydroquinone, the yields of 24 and 25 from the reaction of

N,N-dimethylaniline oxide with aqueous sulfur dioxide are reduced about six fold, with a corresponding increase in the yield of 22.

The reaction of N,N-diethylaniline N-oxide with sulfur dioxide in water at 0°C gave the same types of products, and their yields are given in Table I. Again, there were no appreciable quantities of route B products. The reaction was followed by nuclear magnetic resonance measurements to see if there was any evidence of chemically induced dynamic nuclear polarization (CIDNP) (18) caused by free radical intermediates. No obvious emmission or enhanced absorption could be observed in the ethyl signals of diethylaniline, which after 2 hours made up roughly 20% of the reaction product. However, no evidence of CIDNP from dialkylanilinium ion radical intermediates has yet been reported; it is possible that if the relaxation time for depolarization is fast no effect will be seen. Attempts to demonstrate by electron spin resonance the presence of radicals in the reaction of N,N-dimethylaniline N-oxide with aqueous sulfur dioxide were also fruitless.

However, to date most N,N-dialkylaniline cation-radicals have eluded physical detection because of their rapid coupling reactions with themselves, solvent, or other radicals (19), and we consider that the chemical evidence at the moment is best rationalized by postulating the formation of radical intermediates according to equation [7].

EXPERIMENTAL

Infrared spectra were recorded with a Perkin-Elmer Model 337 spectrophotometer, nuclear magnetic resonance spectra with a Varian A-60 spectrophotometer. Molecular weights were determined using a Mechrolab Model 301A osmometer. All melting points are uncorrected. Analyses were done by Dr. C. Daessle of Montreal and Dr. Alfred Bernhardt of Elbach über Engelskirchen, West Germany.

Materials

The alkaloids, amines, pyridine-sulfur trioxide complex, N,N-dimethylbenzylamine N-oxide (50% aqueous solution), were commercial products. Strychnine N-oxide hydrate, prepared by the method of Bailey and Robinson (20), had m.p. 205-206°C (lit. 207°C (21); after the water of hydration was removed by azeotropic distillation with benzene, it melted at 215-217°C (lit. 216-217° (21)), ν_{max} 958 cm^{-1} (νN-O) (KBr pellet or chloroform solution). Brucine-N-oxide hydrate, prepared in the same manner, had m.p. 123-124°C (lit 124-125°C (21)); after the water of hydration was removed by azeotropic distillation it melted at 197-199°C (lit. 199°C (21)), ν_{max} 958 cm^{-1} (KBr pellet or chloroform solution).

Reaction of N,N-Dimethylbenzylamine N-Oxide with Aqueous Sulfur Dioxide at 0°C.

Sulfur dioxide was bubbled into a solution of N,N-dimethylbenzylamine N-oxide (12g of 50% solution) at

0° for 15 m. The reaction was strongly exothermic. A sticky white precipitate of <u>13</u> was removed, washed with ether, and dried at 80° and 1mm: white powder, ν_{max}^{KBr} 2660 (ν $\overset{+}{N}$-H), 1290 (ν_{asym} SO_3), 1200, 1055 cm^{-1} (ν_{sym} SO_3).

Anal. Calcd. for $C_9H_{13}NO_3S$: C, 50.2; H, 6.1; N, 6.2; S, 14.9. Found: C, 49.9; H, 6.1; N, 6.6; S, 14.4.

Attempts to recrystallize <u>13</u> from water or 95% ethanol resulted in decomposition, and a quantitative yield of benzaldehyde, ν_{max}^{neat} 1695 cm^{-1}, was obtained; its 2,4-dinitrophenylhydrazone melted at 236-237°.

In a second experiment, the reaction mixture was diluted with water (25 ml) to keep <u>13</u> in solution. After reaction the solution was boiled for 5 min. to remove sulfur dioxide, cooled, and extracted with ether (3 x 40ml). The combined ether extracts were dried ($MgSO_4$) and distilled to give benzaldehyde (2.2g, 52%). The aqueous solution was made strongly alkaline and extracted again with ether (3 x 40ml). The combined extracts were dried ($MgSO_4$) and concentrated, and the residue chromatographed on alumina. Elution with benzene separated first N,N-dimethylbenzylamine (1.9g, 35%); n.m.r. spectrum showing singlet (6H) at 2.9δ, and a singlet (2H) at 7.35δ. Next came N-methylbenzylamine (0.4g, 8%), $\nu_{max}^{CHCl_3}$ 3300 cm^{-1} (ν N-H), forming a p-toluenesulfonamide, m.p. 93-95° (reported m.p. 95°).

When the reaction was carried out in the presence of hydroquinone (4.5g), the yields of benzaldehyde (50%), N,N-dimethylbenzylamine (37%), and N-methylbenzylamine (8%) were almost unchanged.

Reaction of Strychnine N-Oxide with Aqueous Sulfur Dioxide at 60-65°C.

Sulfur dioxide was bubbled into a solution of strychnine N-oxide (100 mg) in water (50 ml) at 60-65°C for 15 min. A white precipitate formed within the first 5 min and redissolved as the addition of sulfur dioxide was continued for 10 min. The solution, on treatment with sodium bicarbonate, precipitated strychnine (85 mg; 95%) identified by comparison of m.p. and infrared spectrum with those of an authentic sample.

(N_b-Strychninio) sulfite[3] (15; X=H)

Sulfur dioxide was bubbled through a stirred suspension of anhydrous strychnine N-oxide (2.4 g) in benzene (100 ml) for 4 hours, by which time all suspended solids had gone into solution. Concentration of the solution to 18-20 ml resulted in the separation of a white solid, which crystallized from absolute ethanol as white crystals (1.6 g, 60%), blackening at 194-196°, decomposed at 225°, ν_{max}^{KBr} 1315, 1285, 1110, 1060, 990, 590 cm^{-1}.

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[3] All nomenclature based on "International Union of Pure and Applied Chemistry, Nomenclature of Organic Chemistry, Definitive Rules for Section C", Butterworths, London, 1965, p. 69.

Anal. Calc. for $C_{21}H_{22}O_5N_2S$: C, 60.9; H, 5.3; N, 6.8; S, 7.7; mol. wt. 414. Found: C, 61.0; H, 5.1; N, 6.8; S, 7.7; mol. wt. 410 ± 10 (in benzene, by vapour pressure osmometry).

(N_b-Brucinio) sulfite (<u>15</u>; X=OMe)

The same procedure, applied to the anhydrous N-oxide of brucine, gave the sulfitoamine, blackening at 195°C, decomposed at 22--225°C, ν_{max}^{KBr} 1315, 1285, 1110, 1060, 990, 590 cm^{-1}.

Anal. Calc. for $C_{23}H_{26}N_2O_7S$: C, 58.2; H, 5.5; N, 5.9; S, 8.7. Found: C, 58.3; H, 5.4; N, 6.0; S, 8.8.

Alkaline Hydrolysis of (N_b-Strychninio) sulfite (<u>15</u>; X=H)

(N_b-Strychninio) sulfite (0.12 g), swirled with 0.2N sodium hydroxide (15 ml), went into solution, and in 1-2 mins a white precipitate separated. This was removed by filtration, washed with cold water, and identified as strychnine (0.08 g, 88%), m.p. and mixed m.p. 284-287°C. The filtrate, acidified with HNO_3 and treated with $BaCl_2$, gave a positive sulfate test.

Acid Hydrolysis of (N_b-Strychninio) sulfite (<u>15</u>; X=H)

Sulfur dioxide was bubbled slowly for 15-20 mins through a solution of (N_b-strychninio) sulfite (100 mg) in water (5 ml) at 65-70°. The solution, treated with sodium bicarbonate, deposited strychnine (76 mg, 90%), identified by m.p. and infrared spectrum.

Strychninium-N_b-sulfonate (16; X=H)

(a) By reaction of strychnine-N-oxide with sulfur dioxide in aqueous solution

Sulfur dioxide was bubbled into a solution of strychnine N-oxide (1 g) in water (60 ml) at 0° for 15 mins. A white solid (1 g, 85%), m.p. 265-275°C (dec.), separated which proved identical (infrared spectrum) with the product of the reaction of strychnine with sulfur trioxide (12).

(b) By rearrangement of (N_b-Strychninio) sulfite (15; X=H)

The sulfitoamine 15 (X=H) (0.28 g) was boiled in water (40 ml) for 24 hours. The solution was cooled and the precipitate that separated (0.23 g, 83%) was collected: m.p. 265-275° (dec.), ν_{max}^{KBr} 1250, 1000, 700, 575 cm^{-1}. The product was shown to be identical with 16 (X=H), prepared previously (12), by m.p., infrared spectral comparison, and combustion analysis.

Anal. Calc. for $C_{21}H_{22}O_6N_2S$: C, 60.8; H, 5.3; N, 6.7; S, 7.7. Found: C, 60.6; H, 5.5; N, 6.7; S, 7.5.

When the time of the reaction was reduced to 15 mins impure 16 (X=H), m.p. 260-268° (50% yield) crystallized from the solution on cooling, and impure 15 (X=H), blackening at 189-192°, decomposing at 210-220° (50% yield), was obtained by evaporation of the filtrate at reduced pressure.

Rearrangement of (N_b-Strychninio) sulfite (15; X=H) in the Presence of Hydroquinone

The sulfitoamine 15 (X=H) (0.60 g) was refluxed in water (100 ml) containing hydroquinone (0.17 g) for 24 hours. The solution was cooled and extracted with ether (4 x 60 ml). The ether extracts were dried and evaporated to give residue A (0.14 g). The aqueous layer (pH∿5) was neutralized with sodium bicarbonate. A fine white solid separated and was extracted with chloroform (2 x 50 ml). The chloroform extract was dried and evaporated to give strychnine (0.29 g; 60%); after recrystallization from ethanol, m.p. 286-288° (dec.), undepressed by admixture with an authentic sample of strychnine. The aqueous layer was partially evaporated (25 ml). White needles separated and were collected (0.15 g, 23%), m.p. 265-275°, and were found to be identical with 16 (X=H) by mixed m.p. The aqueous filtrate gave a positive test for sulfite with $BaCl_2$ (0.17 g $BaSO_3$, 53%). Water (40 ml) was added to Residue A, and the mixture was warmed on a steam bath for a few minutes, then cooled. The insoluble yellow material (90 mg) was removed by filtration and recrystallized from ethanol, giving slightly impure benzoquinone, m.p. and mixed m.p. 112-115°. The aqueous filtrate was evaporated and the solid residue (50 mg) recrystallized from ethanol to give needles of hydroquinone, m.p. and mixed m.p. 169-170°.

Reaction of Strychnine N-Oxide with Aqueous Sulfur Dioxide in the Presence of Hydroquinone

Sulfur dioxide was bubbled into a solution of strychnine N-oxide (0.34 gm) and hydroquinone (0.10 gm) in water (40 ml) at 0° for 10 min, during which time a white precipitate separated, redissolved and then a yellow solid separated. The yellow solid after recrystallization from ethanol, had m.p. 113-115°, undepressed by admixture of the sample with an authentic sample of 1,4-benzoquinone. The aqueous solution was extracted with ether (3 x 25 ml) to remove a trace of hydroquinone, and then concentrated to 20 ml, and neutralized with sodium bicarbonate. White needles (0.26 g, 85%), separated; m.p. 286-288° (dec.) after recrystallization from ethanol, and identified by mixed m.p. as strychnine.

Strychnine N-oxide was not reduced to strychnine by hydroquinone in water at 0°.

Acid Hydrolysis of Strychninium-N_b-sulfonate (16; X=H)

(a) 6N Hydrochloric acid

Hydrolysis to strychnine (90% yield) and sulfate ion was complete within 2 min at room temperature.

(b) 0.5N Hydrochloric acid

Hydrolysis complete in about 30 min at room temperature or 1 min at 100°.

(c) Aqueous sulfur dioxide

Hydrolysis was inappreciable after many hours at room temperature, but was complete (95% yield of strychnine) after 15 min at 65-70°.

Alkaline Hydrolysis of Strychninium-N_b-sulfonate (16; X=H)

Strychninium-N_b-sulfonate (0.15 g), swirled with 0.02N sodium hydroxide (18.15 ml), deposited almost immediately strychnine (0.12 g); m.p. 286-288°C (dec.) (identical by IR with an authentic sample of strychnine). The filtrate, acidified with nitric acid and treated with barium chloride, gave a positive sulfate test. Hydrolysis was almost instantaneous with aqueous ammonia and sodium carbonate but was inappreciable with aqueous sodium bicarbonate.

N,N-Dimethylaniline N-Oxide (17) (17,22)

Freshly distilled N,N-dimethylaniline (50 g) was stirred with 10% hydrogen peroxide (450 ml) at 60-70°C for 10 hours. The reaction mixture was cooled and extracted with ether (4 x 100 ml) to remove excess N,N-dimethylaniline. The aqueous layer was partially evaporated under reduced pressure at room temperature. A layer of benzene (100 ml) was added, and the mixture was treated with Linde Molecular Sieves Type 3A (250 g) until there was no positive peroxide test (15 h). The mixture was filtered and the benzene was evaporated. The pale-yellow solid residue was washed with cold benzene, removed by filtration, and dried at reduced pressure. It weighed 38 g (67%) and had m.p. 152-153°C (lit. 152-153°C (22), ν_{max}^{KBr} 965 cm^{-1} (ν N-O), (lit. 960 cm^{-1} (22)).

(N,N-Dimethylanilinio-N) Sulfite (18)

A solution of N,N-dimethylaniline oxide (3.02 g) in anhydrous benzene (100 ml) was saturated with sulfur dioxide. The solution turned yellow-orange, and a dark yellow gum precipitated on the walls of the flask. The benzene solution was decanted. Gradually (10 min) a white solid (18 mg) formed in the benzene solution and was removed by filtration. It had m.p. 95-98°, and an infrared spectrum identical with that of an authentic sample of N,N-dimethylanilinium-N-sulfonate (23) prepared below.

The benzene solution was evaporated under reduced pressure at room temperature. An acid wash of the benzene distillate removed N,N-dimethylaniline (0.75 g, 27%), having an infrared spectrum identical with an authentic sample.

The oily residue in the flask (3.1 g, 70%) was identified as the sulfitoamine 18 by its characteristic infrared spectrum (film between KBr plates: ν_{max} 1320, 1200, 1060, 1010, 780, 695, 580 cm^{-1}). It was very hygroscopic and was not analyzed.

Rearrangement of the Sulfitoamine 18 in Water

The sulfitoamine (3.1 g) was dissolved in water (80 ml) and the solution was kept in an ice-bath for 2 h, or was heated to 70-80° for 30 mins. The solution was then worked up by the procedure of Bamberger and Tschirner (17). Results are given in Table I.

N,N-Dimethylanilinium Sulfonate (23)

Excess sulfur trioxide in 1,2-dichloroethane was added to dry N,N-dimethylaniline (2 g) in 1,2-dichlorethane (50 ml) at 0°. The reaction mixture was stirred for 1 h. The white solid was removed by filtration and dried under reduced pressure: 2.5 g, m.p. 95-99°C (lit. (23) m.p. 85-90°) ν_{max}^{KBr} 1295, 1240, 1200, 1060, 1000, 750, 690, 575 cm^{-1}. The material was very hygroscopic and was hydrolyzed in cold water to N,N-dimethylaniline and sulfate almost instantaneously.

Reaction of N,N-Dimethylaniline Oxide with Aqueous Sulfur Dioxide

(a) Without hydroquinone

Sulfur dioxide was bubbled for 45 mins. into a solution of the oxide (9.98 g) in water (75 ml) at 0°. The resultant emerald-green solution was stirred for 2 days and then worked up according to Bamberger and Tschirner (17).

Results are given in Table 1. Identity of the various products was confirmed by combustion analysis and by their infrared and nuclear magnetic resonance characteristics.

(b) With hydroquinone

The reaction was carried out as above, except that hydroquinone (9 g) was added to the solution of the oxide in water before the introduction of sulfur dioxide. (In a separate experiment, it was shown that hydroquinone did not react with N,N-dimethylaniline oxide in water). After 2 days reaction, the solution was acidified with 2 N sulfuric acid (4.7 ml), and benzoquinone and excess hydroquinone removed by extraction with ether. The solution was then worked up according to the procedure of Bamberger and Tschirner (17), and gave N,N-dimethylaniline (80% yield), N,N-dimethylamino-o-benzenesulfonic acid (10%), N,N-dimethylamino-p-benzenesulfonic acid (3%) and N,N-dimethylamino-o-phenol (1.5%).

N,N-Diethylaniline N-oxide (24)

Freshly distilled N,N-diethylaniline (50 g) was stirred with 10% hydrogen peroxide (450 ml) and methanol (350 ml) at 70° for 48 hours. Excess hydrogen peroxide was decomposed with platinum wire, and methanol was removed by evaporation under reduced pressure. The reaction mixture was extracted with ether (3 x 200 ml) to remove unreacted

N,N-diethylaniline. The aqueous layer was evaporated under reduced pressure at room temperature to give the monohydrate of N,N-diethylaniline N-oxide as pale-yellow residue (30 g 50%), m.p. 89-92°C (lit. 96°C (24)). The monohydrate was used without further purification.

Reaction of N,N-Diethylaniline Oxide with Aqueous Sulfur Dioxide

Sulfur dioxide was bubbled for 45 min into a solution of the N-oxide (10 g) in water (75 ml) at 0°C. The resultant green solution was stirred for 2 days and then worked up according to Bamberger and Tschirner (17). Yields are given in Table I. o-N,N-Diethylaminophenol had m.p. < 20°C (lit. 8-9°C (25)), b.p. 216-219°C (lit. 219-220°C (25)), ν_{max}^{KBr} 3400 cm^{-1} (ν O-H), 1390 cm^{-1}(δ O-H), 1220-1230 (ν C-O), 748 cm^{-1} (ortho substituted). o-N,N-Diethylaminobenzenesulfonic acid darkened at about 275°C and decomposed at 285-310°C (lit.: darkened at 250°C, decomposed above 270°C (26)), ν_{max}^{KBr} 2650 cm^{-1} ($\overset{+}{N}$-H), 1245 cm^{-1} (ν_{asym} SO_3) 1080 cm^{-1} (ν_{sym} SO_3), 765 cm^{-1} (ortho-substituted), 590 cm^{-1} (δ SO_3); n.m.r. in D_2O: 1.20 δ, 6H(CH_3, triplet), 4.02 δ 4H(CH_2, quartet), 7.85 δ, 4H(aromatic broad multiplet).

Anal. Calc. for $C_{10}H_{15}NSO_3$: C,52.4; H,6.6; N,6.1; S,14.0. Found: C,52.6; H,6.7; N,6.0; S,13.9.

p-N,N-Diethylaminobenzenesulfonic acid darkened at 270°C and decomposed at 285-300°C (lit.: darkened at 250°C, decomposed above 270°C (26)), ν_{max}^{KBr} 2650 cm^{-1} (ν $\overset{+}{N}$-H), 1210 cm^{-1}

(ν_{asym} SO_3), 1035 cm^{-1} (ν_{sym} SO_3), 832 cm^{-1} (ortho substituted), 590 cm^{-1} (δ SO_3); n.m.r. in D_2O: 1.20 δ, 6H(CH_3, triplet); 4.02 δ, 4H(CH_2, quartet); 7.85 δ, 4H(aromatic, broad multiplet).

Anal. Calc. for $C_{10}H_{15}NSO_3$ C,52.4; H,6.6; N,6.1; S,14.0. Found: C,52.0; H,6.5; N,6.0; S,14.2.

In a second experiment, the reaction was followed by n.m.r. In acidified D_2O the n.m.r. spectrum of diethylaniline consists of a triplet at 1.45 δ, 6H(CH_3), a quartet at 3.25 δ, 4H(CH_2), and a broad multiplet at 7.85 δ, 5H(aromatic). The spectrum of the N-oxide in D_2O consists of a triplet at 1.20 δ, 6H(CH_3), a quartet at 4.02 δ, 4H(CH_2), and a broad multiplet at 7.85 δ, 5H(aromatic). The alkyl and aryl protons of the ortho and para sulfonic acids had virtually the same chemical shifts as those in the N-oxide.

Sulfur dioxide was bubbled into a solution of the N-oxide at 0°C, and the spectrum was scanned every few minutes for the first hour and then intermittently for 2 days. There was no obvious emmission or enhanced absorption at any time in the alkyl resonances. For the first 20 minutes, the reaction was strongly exothermic so that thermal equilibrium was not established in the probe, and mixing was imperfect (colour not homogeneous), so that during this time the resonances were not well resolved. As the reaction proceeded a well-resolved quartet appeared at 3.25 δ and a triplet at 1.45 δ (slightly obscured by the CH_3 at 1.20 of the N-oxide). After 2 h the quartet at 3.25 integrated to approximately 20% of the quartet at 4.02 δ. The spectrum did not significantly change after this time.

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TABLE I

Yields (%) of products in Scheme 3

REACTION	PRODUCTS			
	19	22	24	25
17 + aq. SO_2 at 0° (ref. 1)	0.6	22	60	20
17 + aq. SO_2 at 0° (this work)	0.5	20	56	18
N,N-Diethylaniline N-oxide + aq. SO_2 at 0°	1.0*	30*	45*	15*
18 in water at 0° - 20°	0.5	20	58	20
18 in water at 70° - 80°	2.9	51	34	9.7

*Et in place of Me in products.

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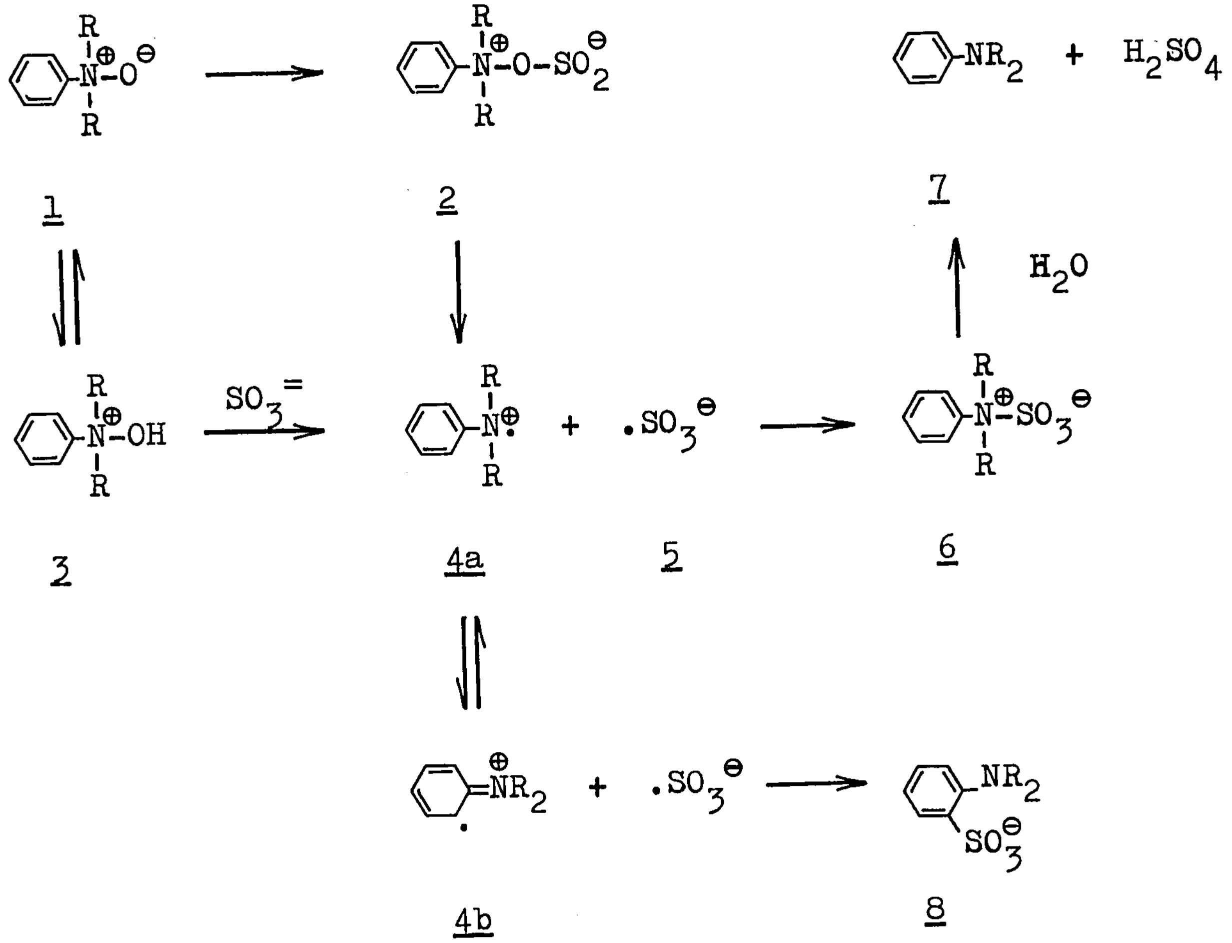
CHAPTER 4

THE REACTION OF HYDROXYLAMINES WITH SULFUR DIOXIDE

The products formed by the reaction of sulfur dioxide with hydroxylamine and with β-phenylhydroxylamine under varying conditions have been studied.

On a etudié les produits fourni par la réaction de la dioxide de soufre avec hydroxylamine et β-phenylhydroxylamine dans les conditions diverse.

In a previous paper (1) we have shown that



SCHEME 1

dimethylaniline N-oxide (<u>1</u>; R=Me) reacts with sulfur dioxide in benzene to give the sulfitoamine <u>2</u> (R=Me). In water the sulfitoamine is converted into the <u>ortho</u>- (<u>8</u>; R=Me) and <u>para</u>-sulfonic acids and dimethylaniline (<u>7</u>; R=Me), the last probably by hydrolysis of the sulfamic acid derivative <u>6</u> (R=Me). The same products are obtained when sulfur dioxide in water reacts with dimethylaniline N-oxide (which under these conditions is probably in the protonated form <u>3</u> (R=Me)).

The intermediacy of the free radicals 4 and 5 in the formation of the sulfonic acids was indicated by the almost total suppression of this reaction by the presence of the free radical scavenger, hydroquinone.

β-Phenylhydroxylamine in weakly acidic solution has the structure 3 (R=H), and so might be expected to react with sulfur dioxide in water like dimethylaniline N-oxide. In fact, Illuminati (2) has already reported the formation of orthanilic acid (8; R=H), aniline (7; R=H) and phenylsulfamic acid (6; R=H) in varying amounts depending on the composition of the solvent (water, ethanol, and 60% ethanol). We have confirmed and extended Illuminati's results, as shown in Table 1. It is apparent that the course of the reaction is considerably more complex than that of dimethylaniline N-oxide; it is difficult, for example, to devise a plausible mechanism for the formation of metanilic acid. Furthermore, the failure of hydroquinone to affect course of the reaction makes it unlikely that the radicals 4 (R=H) and 5 are intermediates of any importance. On the other hand, it seems likely that the protonated form (3; R=H) of β-phenylhydroxylamine is required for reaction; when sodium bisulfite or sodium sulfite was used in place of sulfur dioxide, the rate of reaction became very slow.

In anhydrous ether sulfur dioxide reacted with β-phenylhydroxylamine to form the anilinium salt of phenylsulfamic acid (6; R=H) in fairly good yield instead of the expected sulfitoamine zwitterion (2; R=H). The course of this reaction is difficult to explain and requires further study.

The reaction of hydroxylamine itself with sulfur dioxide in water gives sulfamic acid and small amounts of ammonium bisulfate (3-5). The rate of the reaction is maximal at about neutral pH values, but the ratio of sulfamic acid to ammonium bisulfate in the product is unaffected by pH. It has been concluded (3) that the transition complexes for both reactions have the composition (SO_2, NH_2OH, ψH_2O), but from the effect of pH on rate it is equally possible that the ions of equation [1] are involved:

$$[1] \quad NH_2OH + H_2SO_3 \rightleftharpoons H_3\overset{+}{N}\text{-}OH + HSO_3^-$$

A possible route to sulfamic acid and ammonium bisulfate would then be <u>via</u> the radicals $H_3N^{+\cdot}$ and $\cdot SO_3H$, formed by a reaction of $H_3\overset{+}{N}\text{-}OH$ analogous to that of <u>3</u> (R=Me):

$$[2] \quad H_3\overset{+}{N}\text{-}OH + HSO_3^- \longrightarrow H_3\overset{+}{N}\cdot + OH^- + \cdot SO_3H \longrightarrow$$

$$H_2O + H_3\overset{+}{N}\cdot + \cdot SO_3^- \longrightarrow H_3\overset{+}{N}\text{-}SO_3^-$$

$$\xrightarrow{\text{electron transfer}} \quad NH_3 + SO_3 \longrightarrow \text{ammonium bisulfate}$$

However, we have found the ratio of the products in this reaction to be unaffected by the presence of hydroquinone; this would have been expected (1) to reduce the ion-radicals of equation [2], and hence to favour the formation of ammonium ion at the expense of sulfamic acid. An intramolecular rearrangement of sulfitoammonium ion (cf. ref. 6) is accordingly indicated.

EXPERIMENTAL

Infrared spectra were recorded with Perkin-Elmer Model 337 and Model 257 spectrophotometers. All melting points are uncorrected. Analyses were done by Dr. C. Daessle of Montreal and Dr. Alfred Bernhardt of Elbach über Engelskirchen, West Germany.

Materials

Hydroxylamine hydrochloride, orthanilic, metanilic and sulfanilic acids were commercial products. Phenylhydroxylamine, m.p. 81-82°C (lit. 83-84°), was prepared by the reduction of nitrobenzene by zinc in aqueous ammonium chloride (7). Freshly prepared material was always used because the compound decomposed slowly on standing. Phenylsulfamic acid, isolated as the phenylammonium salt melted with sublimation at 180°, ν_{max}^{KBr} 2560 cm^{-1} ($\nu \overset{+}{N}H_2$), 1200 cm^{-1} ($\nu_{asym}SO_3$), 1010 cm^{-1} ($\nu_{sym}SO_3$), 750 and 690 cm^{-1} (monosubstituted benzene) 695 cm^{-1} (νS-N), 575 cm^{-1} (δSO_3), or as the barium salt ν_{max}^{KBr} 1210-1160 1200 cm^{-1} ($\nu_{asym}SO_3$), 1060 cm^{-1} ($\nu_{sym}SO_3$), 750 and 690 cm^{-1} (monosubstituted benzene) 670 cm^{-1} (νS-N), 580 cm^{-1} (δSO_3) was prepared by the procedure of Traube (8). Acidification of the barium salt resulted in hydrolysis to aniline bisulfate.

Reaction of Hydroxylamine with Aqueous Sulfur Dioxide

Sulfur dioxide was bubbled into 1 <u>M</u> aqueous hydroxylamine hydrochloride (50 ml) for 30 m at 0°C, and the solution was stirred for another 60 m. Evaporation of the solution to dryness gave a white crystalline residue (4.9g). ν_{max}^{KBr} 3100-2600 cm^{-1} ($\nu\overset{+}{N}H_4$ and $\overset{+}{N}H_3$), 1540 cm^{-1} ($\delta_{deg}NH_3$), 1445 cm^{-1} ($\delta_{sym}NH_3$), 1300 cm^{-1} ($\nu_{deg}SO_3$), 1160 cm^{-1} ($\nu_{asym}SO_3$ in HSO_4^-), 1065 cm^{-1} ($\nu_{sym}SO_3$), 842 cm^{-1} (νS-O(H) in HSO_4^-), 688 cm^{-1} (νS-N). The relative intensities of the sulfamic acid peak at 688 cm^{-1} (9) and the bisulfate peak at 842 cm^{-1} (10), by comparison with those of known mixtures of sulfamic acid and potassium bisulfate, indicated an approximately 9:1 ratio of sulfamic acid: ammonium bisulfate, in agreement with results in the literature (3). The ratio was not affected when the reaction was repeated in the presence of hydroquinone (5.6g), which was removed after the reaction by extraction with ether.

Reaction of Phenylhydroxylamine with Sulfur Dioxide

Through a solution of phenylhydroxylamine (5g) in absolute alcohol (60 ml) at 10-25°C, dry sulfur dioxide was passed for 1-2h with stirring. A white crystalline solid was gradually formed and the color of the solution changed from light tan to brown. The flask was stoppered and allowed to stand for 3-30 hours at 10° (different times caused no significent difference in yields). The mixture was filtered and the collected solid was found by infrared examination to be a crude mixture of orthanilic and sulfanilic acids. This mixture was separated by fractional crystallization from water. The *para* isomer was crystalized first; it decomposed above 180° (lit 188° (25)) and its infrared spectrum (ν_{max}^{KBr} 1230-1180 cm^{-1} ($\nu_{asym}SO_3$), 1025 cm^{-1} ($\nu_{sym}SO_3$), 770 and 705 cm^{-1} (ortho substituted benzene), 560 cm^{-1} (δSO_3)) was identical with that of an authentic sample.

The original mother liquor from the o- and p-isomers was made alkaline with potassium hydroxide and was extracted with ether (4x50 ml). The ether extracts contained aniline, which was identified by comparison of its infrared spectrum and its chromatographic properties on alumina with those of an authentic sample. The extracted aqueous layer was neutralized with dilute hydrochloric acid and evaporated to give a brown solid. This was extracted with hot absolute alcohol (4x50 ml), then the solid was extracted with hot 90-95% alcohol (4x50 ml), after which the residue consisted of inorganic material only. Evaporation of the absolute alcohol extracts gave a dark-colored solid which was recrystallized from water (charcoal) to give white crystals of metanilic acid, decomposing above 210°, ν_{mas}^{KBr} 1240-1150 cm^{-1} ($\nu_{asym}SO_3$), 1025 cm^{-1} ($\nu_{sym}SO_3$), 790 and 700 cm^{-1} (meta substituted benzene), 560 cm^{-1} (δSO_3), identical with the spectrum of an authentic sample. From the 90-95% alcohol extracts, white crystals separated whose infrared spectrum (ν_{max}^{KBr} 1210-1160 cm^{-1} ($\nu_{asym}SO_3$), 1055 cm^{-1} ($\nu_{sym}SO_3$), 750 and 690 cm^{-1} (mono substituted benzene), 675 cm^{-1} (νS-N), 580 cm^{-1} (δSO_3)) showed them to be potassium phenylsulfamate, by comparison with the spectrum of an authentic specimen of the barium salt. Potassium phenylsulfamate was readily soluble in cold water to give a neutral solution which gave no test for sulfate ion; when this solution is made acid and heated, complete hydrolysis of the product was effected, so that addition of barium chloride yielded an abundant precipitate of barium sulfate, and neutralization of the aqueous phase with sodium bicarbonate and extraction with ether removed aniline quantitatively.

The same procedure was followed with other solvents (water and 60% ethanol) for the reaction. The yields of the various products are reported in Table 1.

Reaction of Phenylhydroxylamine with Sulfur Dioxide in the Presence of Hydroquinone

The same procedure as above was followed, except that hydroquinone (6 g) was added at the start of the reaction. Both the white solid formed initially and the filtrate from it were extracted with ether to remove a cream-colored solid (5.6 g, 93%), m.p. 169-171°, which was mainly hydroquinone, (lit. m.p. 171-172°). A trace of benzoquinone (about 5%), was detected by comparing the chromatographic properties of the product on silica gel with the properties of known mixtures of hydroquinone and benzoquinone.

Reaction of Phenylhydroxylamine with Sulfur Dioxide in Anhydrous Ether

Dry sulfur dioxide was bubbled into a solution of phenylhydroxylamine (2.5 g) in anhydrous ether (50 ml) at 0°C for 45 min. In the first few seconds a white precipitate formed, which then darkened to an orange oil and then (within a few minutes) to a black gum. The mixture was stirred for 8-10 hours, by which time the black gum had solidified on the walls of the flask and a greyish powder was suspended in the ether. The grey powder (1.4 g, 42%), collected by filtration, sublimed at about 1180° and was identified as anilinium phenylsulfamate by comparison of its infrared spectrum (ν_{max}^{KBr} 2560 (ν $\overset{+}{N}H_2$), 1200 (ν_{asym} SO_3), 1010 (ν_{sym} SO_3), 750 and 690 (mono-substituted benzene), 625 (ν S-N), and 575 cm^{-1} (δ SO_3)) with the spectrum of an authentic specimen.

Anal. Calcd. for $C_{12}H_{14}N_2O_3S$: C, 54.1; H, 5.3; N, 10.5; S, 12.0. Found: C, 54.3; H, 4.9; N, 10.3; S, 12.4.

The powder (1 g) was heated with 2N hydrochloric acid to 75° for 10 m, and the resultant solution then neutralized with sodium bicarbonate and extracted with ether, removing aniline (0.55 g, 90%). The aqueous layer, acidified with nitric acid, gave a positive test for sulfate with barium chloride.

The ether filtrate was evaporated to give slightly impure aniline (25 mg, 1.5%), identified by comparison of infrared characteristics and chromatographic properties on alumina with those of an authentic sample of aniline. The black sticky solid deposited on the walls (1.8 g, 54%) was identified by its infrared spectrum as impure anilinium phenylsulfamate.

Reaction of Phenylhydroxylamine with Sodium Bisulfite in 60% Alcohol

A solution of sodium bisulfite (5 g) and phenylhydroxylamine (2.5 g) in 60% alcohol (80 ml) was stirred for 4 days at room temperature away from contact with air. Crystals that had gradually formed (0.3 g, 7.5%) were identified as a mixture of orthanilic and sulfanilic acids by its infrared spectrum. Alcohol was removed from the filtrate by evaporation, and the aqueous layer was extracted with ether (4x75 ml). The combined ether extracts were dried and evaporated to give phenylhydroxylamine (2.2 g, 88%), m.p. 80-81°, and a trace of aniline.

Reaction of Phenylhydroxylamine with Sodium Sulfite in 60% Alcohol

A mixture of phenylhydroxylamine (2.5 g) and sodium sulfite (6 g) in 60% alcohol (100 ml) was stirred out of contact with air for 4 days at room temperature (sodium sulfite was not completely soluble). The reaction mixture was filtered, and the solid residue was extracted with hot alcohol (4x60 ml). Evaporation of the alcohol extracts gave a mixture of orthanilic and sulfanilic acids (0.2 g, 5%), contaminated by a trace of sodium sulfite. Alcohol was removed from the filtrate by evaporation, and the aqueous solution was extracted with ether (4x75 ml). The combined ether extracts were dried and evaporated to give a crude product (2.3 g) containing phenylhydroxylamine, aniline, azoxybenzene, and unidentified products, as shown by comparison of the chromatographic properties on alumina with those of authentic samples.

The financial support of the National Research Council of Canada is gratefully acknowledged.

TABLE 1

Effect of solvent and of the presence of hydroq
products from the reaction of phenylhydroxylami

Solvent	Aminobenzenesulfonic Acids		
	ortho-	meta-	para-
EtoH	35	5	10
EtOH (+S)	35	5	10
60% EtOH	20	3-5	15
60% EtOH (+S)	20	3-5	12
Water	15-20	1-3	12
Water (+S)	15-20	1-3	12

TABLE 1

ence of hydroquinone (S) on the yields (%) of the nylhydroxylamine with sulfur dioxide.

zenesulfonic Acids		Aniline	Phenylsulfamic Acid
meta-	para-		
5	10	45	1-2
5	10	45	1-2
3-5	15	40	10-15
3-5	12	42	10-15
1-3	12	20	40
1-3	12	20	40

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CHAPTER 5

FORMATION AND HYDROLYSIS OF SULFATOAMINES

Sulfatoamines are formed by reaction of amine oxides with pyridine-sulfur trioxide complex, and are hydrolized by aqueous alkali to the amine oxide and sulfate ion.

La réaction des oxides d'amines avec la complexe de pyridine et de trioxide de soufre fournit les sulfatoamines; celles-ci sont hydrolysés en milieu alcalin aux oxides d'amine et ion sulfate.

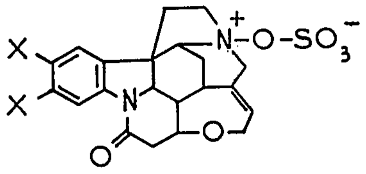
Lecher and Hardy (1) obtained triethylammonio sulfate (2) from the reaction of triethylamine oxide with triethylamine-sulfur trioxide complex, and from the reaction of triethylamine with sulfur dioxide in benzene, triethylammonio sulfite (1) probably being an intermediate in the latter reaction:

[1] 

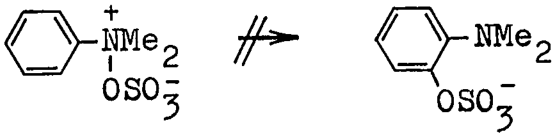
$$\mathrm{Et_3\overset{+}{N}\text{-}O^-}\quad \mathrm{\bar{O}_2S\text{-}O\text{-}\overset{+}{N}Et_3} \longrightarrow \mathrm{Et_3\overset{+}{N}\text{-}O\text{-}SO_3^-} + \mathrm{NEt_3}$$

1 2

In a similar fashion, we have obtained the sulfatoamines 3 (X=H and OMe) from the reactions of the pyridine-sulfur trioxide complex with strychnine N-oxide and brucine N-oxide, and 4 from the reaction with dimethylaniline N-oxide.



3



4 5

All of these sulfatoamines were hydrolyzed in water or in alkaline solution to sulfate ion and the amine oxide (in contrast to 2, which under these conditions gave diethylamine, acetaldehyde, and sulfate ion (1)).

The failure of 4 to rearrange to 5 shows that it cannot be an intermediate in the Boyland-Sims reaction of dimethylaniline with alkaline persulfate to give 5 (2); the latter is most probably formed by electrophilic attack of persulfate ion at the *ortho* position by a mechanism reminiscent of the Elbs persulfate oxidation of phenols (3). However, such a finding does not eliminate the possibility that the alkaline persulfate oxidation of aromatic *primary* amines may go through an intermediate analogous to 4; evidence supporting this possibility has been advanced recently (4).[1]

Experimental

Infrared spectra were recorded with a Perkin-Elmer Model 337 spectrophotometer and nuclear magnetic resonance spectra with a Varian A-60 spectrophotometer. Analyses were done by Dr. C. Daessle of Montreal and Dr. Alfred Bernhardt of Elbach über Engelskirchen, West Germany.

Materials

The alkaloids, N,N-dimethylaniline, and pyridine-sulfur trioxide complex were commercial products. Strychnine N-oxide hydrate, prepared by the method of Bailey and Robinson (5), had m.p. 205-206°C (lit. 207°C (6)); after the water of hydration was removed by azeotropic distillation with benzene, it melted at 215-217°C (lit. 216-217°C (6)), ν_{max} 958 cm^{-1} (νN-O) (KBr pellet or chloroform solution).

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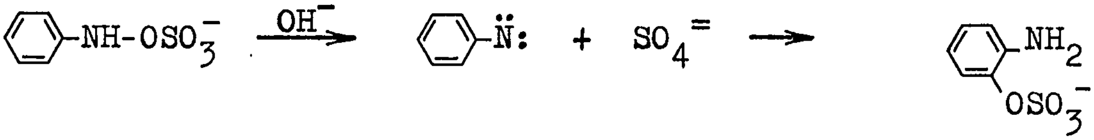
[1] A nitrene is a plausible further intermediate:



Brucine N-oxide hydrate, prepared in the same manner, had m.p. 123-124°C (lit. 124-125°C (6)); after the water of hydration was removed by azeotropic distillation it melted at 197-199°C (lit. 199°C (6), ν_{max} 958 cm^{-1} (KBr pellet or chloroform solution). N,N-Dimethylaniline N-oxide, prepared by the method of Bamberger and Tschirner (7), had m.p. 152-153°C (lit. 152-153°C (7)) ν_{max}^{KBr} 965 cm^{-1} (νN-O) (lit. 960 cm^{-1}(8)).

(N_b-Strychninio) sulfate (3; X=H)

Pyridine-sulfur trioxide complex (0.27 g) was added to anhydrous strychnine-N-oxide (0.6 g) in dry pyridine (25 ml), and stirred for 5 min. The white solid (0.6 g, 83%) that separated was removed by filtration and freed from pyridine by pumping at 2 mm. It blackened at 200-202°C, melted at 228-230°C, ν_{max}^{KBr} 1335, 1295, 1120, 1060, 710, 622 cm^{-1}.

Anal. Calc. for $C_{21}H_{22}O_6N_2S$: C, 58.6; H, 5.2; N, 6.5; S, 7.4. Found: C, 58.6; H. 5.4; N, 6.5; S, 7.4.

(N_b-Brucinio) sulfate (3; X=OMe)

The same procedure applied to brucine-N-oxide gave 5 (X=OMe), blackening 205-207°C, melts at 235-236°C, ν_{max}^{KBr} 1335, 1295, 1129, 1060, 710, 622 cm^{-1}.

Anal. Calc. for $C_{23}H_{26}O_8N_2S$: C, 56.3; H, 5.3; N, 5.7; S, 6.5. Found: C, 56.3; H, 5.4; N, 5.7; S, 6.3.

Alkaline Hydrolysis of (N_b-strychninio) sulfate)

(N_b-strychinio) sulfate (0.1 g), swirled with 0.2N sodium hydroxide (10-15 ml), went into solution. Repeated extraction with chloroform (10x25 ml) removed strychnine N-oxide hydrate (55 mg, 64%) (identified by m.p., infrared spectrum and thin-layer chromatography. The aqueous phase, acidified with nitric acid and treated with barium chloride, gave a positive sulfate test.

(N,N-Dimethylanilinio) Sulfate (4)

Pyridine-sulfur trioxide complex (0.68 g) was stirred for 30 min with anhydrous N,N-dimethylaniline N-oxide (0.6 g) dissolved in dry pyridine (30 ml). Thin-layer chromatography on alumina then showed that no N-oxide (R_f 0.75 in $CHCl_3$/EtOH 80/20) remained. An oily gum formed on the walls of the flask. The solution was decanted, and the residual gum, dried under reduced pressure, set to a pale yellow solid (0.9 g), very hygroscopic. The infrared spectrum (ν_{max}^{KBr} 1340, 1275, 1110, 1030, 755, 685, 615 cm^{-1} was similar to that of (strychninio-N_b) sulfate.

Anal. Calc. for $C_8H_{11}O_4NS$: C, 44.2; H, 5.1; N, 6.4; S, 14.7. Found: C, 44.4; H, 5.3; N, 6.4; S, 14.5.

Hydrolysis of (N,N-Dimethylanilinio) Sulfate in Water

The sulfate (0.99) in water (25 ml) was heated on a steam bath for 10 min. The solution was neutralized with sodium bicarbonate, and was extracted with chloroform (10x40 ml). The extracts were dried and evaporated to give N,N-dimethylaniline-N-oxide (0.45 g), $\nu_{max}^{CHCl_3}$ 965 cm^{-1}, R_f 0.75 by thin-layer chromatography. The acidified aqueous solution gave a positive test for sulfate (0.95 g $BaSO_4$; 98%). Picric acid added to the aqueous solution gave a yellow precipitate (0.17 g) of N,N-dimethylaniline oxide picrate, m.p. 136-138° (lit. m.p. 136° (7)).

We gratefully acknowledge the financial support of the National Research Council of Canada.

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PART B

RING-CHAIN TAUTOMERISM OF HYDROXYKETONES

CHAPTER 6

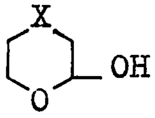
RING-CHAIN TAUTOMERISM OF HYDROXYKETONES

ABSTRACT

A study of the ultraviolet, infrared and nuclear magnetic resonance spectra of 5-hydroxy-2-pentanone and of 6-hydroxy-2-hexanone has shown that in most organic solvents there is a slight preference for the open-chain form of the hydroxyketone over the cyclic hemiketal. Increase in temperature and highly polar organic solvents favor the open-chain tautomer; in water there was no evidence of any cyclic form.

L'étude des spectres d'absorption infra rouge, ultraviolet et de résonance magnétique nucléaire des composés 5-hydroxy-2-pentanone et 6-hydroxy-2-hexanone a montré que dans la plupart des solvants organiques la forme ouverte de l'hydroxycétone est légèrement préférée à la forme cyclique de l'hémicétal. L'augmentation de la température ainsi que de la polarité du solvant favorise l'existence de ces composés sous la forme ouverte.

Ring-chain tautomerism involving hydroxyl and carbonyl functions is well established (1). The best known examples are aldoses and ketoses, such as glucose and fructose (2). Other examples exist where the carbon chain is broken by a heteroatom as in equation 1, where X = N,O,S (3).

[1] $HO-CH_2-CH_2-X-CH_2-CHO \rightleftharpoons$ 

Evidence from the early literature showed that γ- and δ- hydroxyaldehydes and ketones reacted both as the straight chain form and as the cyclic hemiacetal or hemiketal (4,5), but no quantitative data were available on the equilibrium constants of the ring-chain tautomerism.

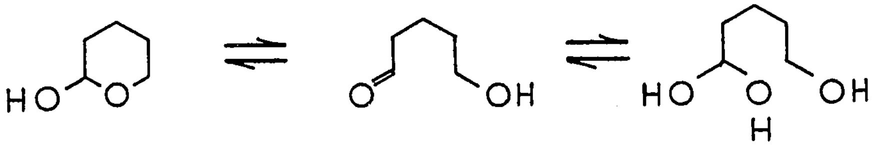
More recently, reliable estimates of the equilibrium constants for variously substituted α- (β-hydroxyethyl)-amino desoxybenzoins (1) and the corresponding cyclic hemiketals (2) in various solvents have been obtained from ultraviolet and infrared measurements (6,7).

[2] 

1 2

Hurd and Saunders (8) showed, by a study of the ultraviolet spectra of ω-hydroxyaldehydes, that in 75% aqueous dioxane 4-hydroxybutanal and 5-hydroxypentanal exist predominantly as the cyclic hemiacetals, containing only 11.4 and 6.1%, respectively, of free aldehyde. It is likely that besides the lactol form, 2-3% of the hydrated aldehyde (9,10) is also present.[1]

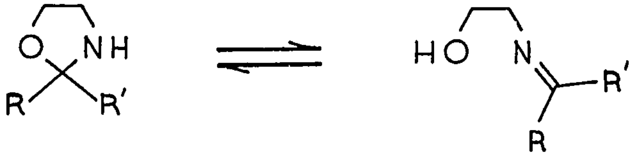
[3]



Substitution of the lactol stabilizes it with respect to the open-chain tautomer (13), which at equilibrium is present to only a very minor extent in solutions of the common pentoses and hexoses (14) because of the operation of various conformational effects (12b, 15).

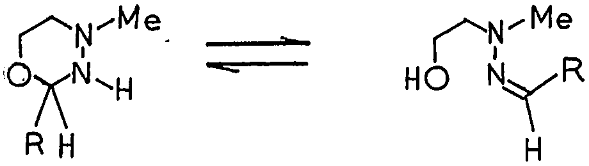
Although there are no quantitative data on the ring-chain tautomerism of simple hydroxyketones, there is a fair amount of quantitative data on the ring-chain tautomerism of hydroxy-imines, such as oxazolidines (3a) in equilibrium with their corresponding acyclic Schiff bases (3b) (16). Dorman (17), by a NMR study, has given a good account of the effect on the ring-chain tautomerism of hydroxy-hydrazones (4a ⇌ 4b)

[4]



3a 3b

[5]



4a 4b

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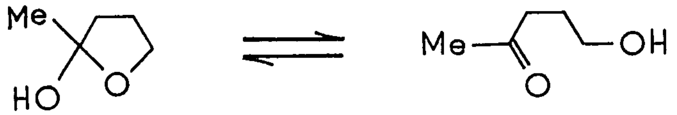
[1] From the infrared spectrum in carbon tetrachloride solution, approximate values of 3.0% and 4.5% can be obtained (11, 12a).

of size of substituents, temperature, and solvent polarity. Cyclic structures have been postulated for the phenylhydrazones of some pyranoses (18), and for the 2,4-dinitrophenylhydrazone of a steroidal δ-hydroxyaldehyde (13).

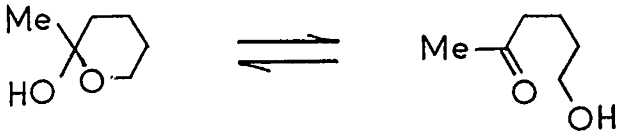
In the present paper we present a study of various parameters (ring size, temperature, and solvent polarity) on the equilibrium constants for the systems 5-hydroxy-2-pentanone (6) ⇌ 2-methyl-2-hydroxytetrahydrofuran (5) equation 6), 6-hydroxy-2-hexanone (8) ⇌ 2-methyl-2-hydroxytetrahydropyran (7) (equation 7), and the corresponding 2,4-dinitrophenylhydrazones (equations 8 and 9).

[6]



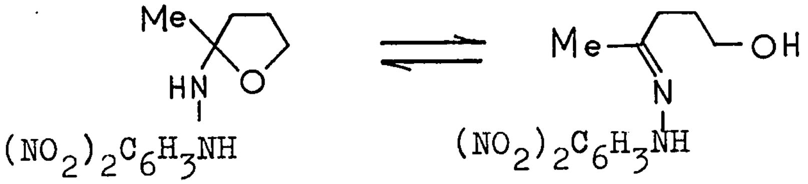
5 6

[7]



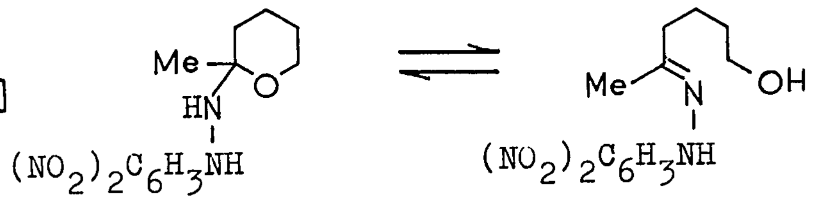
7 8

[8]



9

[9]



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EXPERIMENTAL

Infrared spectra were recorded with Perkin-Elmer Model 337 and 257 spectrophotometers for routine, and with Model 521 for quantitative work. Nuclear magnetic resonance spectra were recorded with a Varian A-60 spectrophotometer and ultraviolet spectra with a Unicam SP800 spectrophotometer equipped with a temperature-controlled cell block. Analyses were done by Dr. C. Daessle of Montreal and Dr. A. Bernhardt of Elbach über Engelskirchen, West Germany.

Materials

Starting materials were commercial products. Wherever possible spectrograde solvents were used. For the ultraviolet spectra these were cyclohexane, dioxane, acetonitrile, carbon tetrachloride, chloroform and methanol. Absolute ethanol, 95% ethanol, freshly distilled water, and freshly distilled reagent grade dimethylsulfoxide, kept over Linde Molecular Sieves Type 3A, were also used. Spectrograde carbon tetrachloride was used as solvent for the quantitative infrared measurements. Deuterated solvents for NMR were obtained from Stohler Isotope or Merck, Sharpe and Dohme.

5-Hydroxy-2-Pentanone (6)

4,5-Dihydro-2-methylfuran (10g) was refluxed for 45 m in 0.02N hydrochloric acid (40ml) until the solution was homogeneous. The solution was cooled and saturated with anhydrous potassium carbonate. The oil that separated was extracted with ether (5 x 20ml). The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and evaporated at reduced pressure at room temperature to give a slightly pale yellow liquid (10.9g, 90%). The product was distilled twice at 10^{-3}mm and a bath temperature of 35° and condensed on a cold finger cooled by dry ice-ethanol. The distillate was a clear colorless liquid, ν_{max}^{neat} 3440 (ν O-H), 1720 (ν C=O), 1170 (ν C-O of 5), and 1075cm^{-1} (ν C-O of 6).

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.8; H, 9.9. Found: C, 58.6; H, 9.7.

The 2,4-dinitrophenylhydrazone 9, recrystallized twice from ethanol and dried at reduced pressure, had m.p. 150-151°, ν_{max}^{KBr} 3500 (ν O-H), 3330 (ν N-H), 1625 (ν C=N), and 1130cm^{-1} (ν C-O); λ_{max}^{EtOH} 362nm (ϵ =21,000), $\lambda_{max}^{acetone}$ 366nm (ϵ = 20,000); NMR in DMSO-d_6: 2.1ppm (s,3H,CH_3), 7.7-9.0ppm (m, 3H,Ar).

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.8; H, 5.0; N,19.9. Found: C, 46.6; H, 5.2; N, 20.2.

6-Hydroxy-2-hexanone (8)

The hydroxy-ketone was prepared in similar fashion in 90% yield from hydrolysis of 2-methyl-5,6-dihydropyran-3-carboxylic acid (10g, m.p. 118-119°, lit. 119° (4)), obtained by the method of Perkin (4). The product was a clear colorless liquid, ν_{max}^{neat} 3430 (ν O-H), 1725 (ν C=O), 1095 (ν C-O of 7), 1045cm^{-1} (ν C-O of 8).

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.0; H, 10.4. Found: C, 62.2; H, 10.5.

The 2,4-dinitrophenylhydrazone 10, recrystallized twice from ethanol and dried at reduced pressure, had m.p.

84-85°, $\nu_{\max}^{\mathrm{KBr}}$ 3460 (νO-H), 3330 (νN-H), 1618 (νC=N), 1595 (Ar) and 1110cm^{-1} (νC-O); $\lambda_{\max}^{\mathrm{EtOH}}$ 362nm (ϵ=21,000), $\lambda_{\max}^{\mathrm{acetone}}$ 366nm (ϵ = 20,000); NMR in DMSO-d_6: 2.1 ppm (s,3H,CH_3), 7.8-9.0ppm (m,3H,Ar).

Anal. Calcd. for $C_{12}H_{16}N_4O_5$: C, 48.6; H, 5.4; N, 18.9. Found: C, 48.7; H, 5.3; N, 19.1.

2-Methoxy-2-methyltetrahydrofuran 11 (19)

4,5-Dihydro-2-methylfuran (6g) was refluxed for 30m with methanol (6ml) and glacial acetic acid (2 drops). The reaction mixture was made basic with sodium methoxide and filtered. The excess methanol was evaporated at reduced pressure and the solution was again filtered. The residue was distilled, and the fraction boiling at 115-116° (lit. 116° (19)) was collected. It was a clear colorless liquid, $\nu_{\max}^{\mathrm{neat}}$ 2840 (C-H of OMe), 1075 (νC-O) and 1035cm^{-1} (νC-O); NMR in CCl_4: 1.35ppm (s,3H,CH_3), 3.1ppm (s, 3H, CH_3O); end absorption only in the ultraviolet.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.0; H,10.4. Found: C, 62.1; H, 10.3.

5-Ethoxy-2-pentanone (12)

This compound was prepared by reported methods (20, 21). The clear colorless liquid, b.p. 169-170° (lit. 170-171° (20)), was purified for ultraviolet spectral work by vapor phase chromatography on an Aerograph 705 Autoprep with 1/12 effluent splitter. The column consisted of 30% SE-30 on Chromosorb W, 20 ft aluminum, 3/8" d; H_2 flow 25ml/m, N_2 flow in detector 25ml/m, N_2 flow in collector 300ml/m; column temperature 175°, injector 215°, detector 250°. The liquid had ν_{max}^{neat} 2875 (C-H of OEt), 1721 (νC=O), and 1120cm^{-1} (νC-O); $\lambda_{max}^{cyclohexane}$ 278nm (ϵ =17.0), λ_{max}^{EtOH} 273nm (ϵ =19.5), $\lambda_{max}^{H_2O}$ 265nm (ϵ = 24.6); NMR in CCl_4: 1.1ppm (t,3H,CH_3 of OEt), 1.8ppm (m,2H,CH_2), 2.1ppm (s,3H,CH_3),2.5ppm (t,2H,CH_2), 3.35ppm (t,2H,CH_2), 3.4ppm (q,2H,CH_2).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.8. Found: C, 64.6; H, 10.6.

The 2,4-dinitrophenylhydrazone of 12, recrystallized twice from ethanol and dried at reduced pressure, had m.p. 155-156°, ν_{max}^{KBr} 3320 (νN-H), 1628 (νC=N), 1595 (Ar) and 1135cm^{-1} (νC-O); λ_{max}^{EtOH} 362nm (ϵ =21,000), $\lambda_{max}^{acetone}$ 366nm (ϵ =20,000); NMR in DMSO-d_6: 1.2ppm (t,3H,CH_3 of OEt), 2.1ppm (s,3H,CH_3), 7.8-9.0ppm (m,3H,Ar).

Anal. Calcd. for $C_{12}H_{16}N_4O_5$: C, 55.3; H, 6.4; N, 9.9. Found: C, 55.5; H, 6.4; N, 9.8.

Analytical Procedures

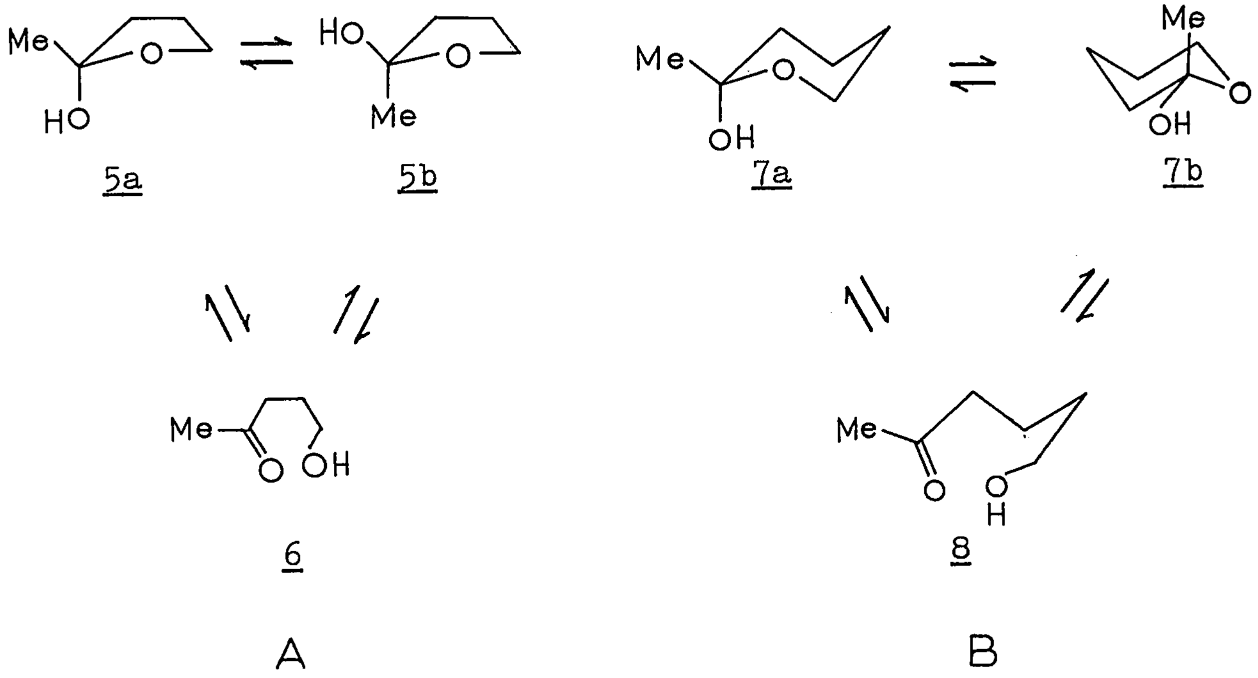
For infrared studies, the intensities of the carbonyl absorption at 1721cm^{-1} of equilibrated solution (0.005 to 0.04M) of $5 \rightleftharpoons 6$ in carbon tetrachloride were compared with those of standard solution of compound 12 (Compound 11 had no absorption in this region). These indicated 57.7 ± 0.5% of the keto form 6 in carbon tetrachloride.

For NMR studies, 1-2M solutions of $5 \rightleftharpoons 6$ and $7 \rightleftharpoons 8$ in carbon tetrachloride, cyclohexane-d_{12}, chloroform-d, acetone-d_6, ethanol-d_6, acetonitrile-d_3, dimethylsulfoxide-d_6, deuterium oxide and formamide (for $\underline{5} \rightleftharpoons \underline{6}$ only), were equilibrated at 37° ± 0.5° for 5h (equilibrium of most samples was reached within a few minutes, in contrast to the equilibrations of Hurd and Saunders (8)). The spectra were recorded with probe temperature 37° ± 1°, sweep width 250cps. At least duplicate samples of each concentration and solvent were recorded, the integration of each spectrum was an average of 5 scans. Relative concentrations of the cyclic and open-chain forms were calculated from the integrations of the two singlet methyl groups, the one at lower field being the methyl group of the open-chain form. Results are recorded in Tables 1 and 2.

For the ultraviolet study, 0.02 to 0.05$\underline{M}$ solutions of $\underline{5} \rightleftharpoons \underline{6}$ and $\underline{7} \rightleftharpoons \underline{8}$ were equilibrated in water baths maintained at 15.0° ± 0.1°, 24.8 ± 0.1°, and 50.1° ± 0.1°, the temperature of samples in the cell block (i.e., the temperatures at which the spectra were recorded) were 15.4° ± 0.1°, 25.0° ± 0.1°, and 49.8° ± 0.2°. Samples were equilibrated for 5h (15m was in fact enough for most samples). The equilibria were very mobile and no acid was required. The hydroxyketones and model compound $\underline{12}$ had a band in the region 265 → 280nm depending on the solvent or solvent mixture. Compound $\underline{11}$, a model for the cyclic forms, had no absorption in that region. The extinction coefficients of the hydroxyketones were compared with those of compound $\underline{12}$ in each solvent and solvent mixture, at each temperature. Results are recorded in Tables 1, 2, 3, 4, 5 and 6. At least two runs and usually three or four, were made for each determination.

RESULTS AND DISCUSSION

There are two possible diastereomeric species associated with the cyclic tautomers 5 and 7 originating at the 2-positions by virtue of the direction of ring closure. The chain tautomers exist in one form only. The different species and their possible interrelation are outlined in Schemes 1A and 1B.

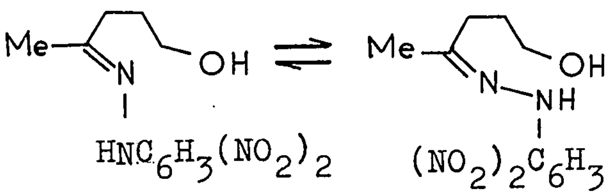


SCHEME I

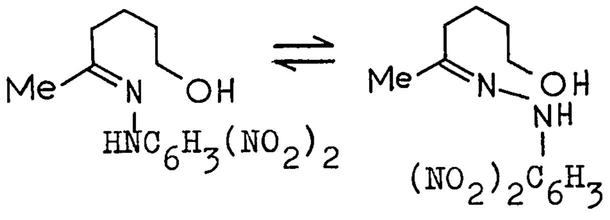
The difference in the free energy content of 5a and 5b may not be pronounced because the five-membered ring is quite flexible (22); this flexibility does not allow calculations of interaction energies similar to those applied to the more rigid chair form (12b) of cyclohexane. Structure 7a (OH axial) is favored over 7b because of the anomeric effect (23). This effect, a dipolar interaction, has been found by experiment and calculations to be approximately 1.3-1.7 kcal/mole in nonpolar solvents (24, 25, 26). The value falls as low as 0.9 kcal/mole in aqueous methanol, and the anomeric effect on free hydroxyl groups in aqueous solution is even smaller. Solvents of high dielectric constant reduce the strength of the anomeric effect (12c, 27).

Inspection of the NMR spectra of the systems $5 \rightleftharpoons 6$ and $7 \rightleftharpoons 8$ showed only two methyl signals, one for the open-chain keto form (at lower field) and one for the cyclic form. From this, it may be concluded that either the respective methyl groups of 5a and 5b and of 7a and 7b have about the same chemical shifts, or that the conformational equilibrium between the cyclic forms is sufficiently fast that only a single weight-average absorption is observed. The latter assumption is more tenable (12b).

If the 2,4-dinitrophenylhydrazones 9 and 10 exhibit any ring-chain tautomerism, the cyclic isomers could exist in two forms; additionally, the open-chain tautomer can exist in two geometric isomeric forms, *syn* (9a, 10a) and *anti* (9b, 10b).

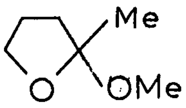


9b 9a

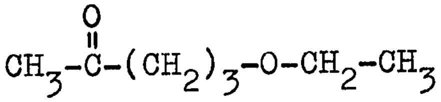


10b 10a

Interconversions of *syn* and *anti* isomers of simple hydrazones can generally be induced with heat or light with relative ease (17). At equilibrium the *anti* form should predominate because of steric hindrance experienced by the *syn* form. Because of the facile equilibrium between these two forms, the NMR spectra would be expected to show only one methyl resonance for the open-chain form (17). In fact, in DMSO-d_6 no evidence was found for any cyclic forms, only a singlet at 2.1ppm for the methyls of the open-chain forms 9 or 10 being observed. The infrared spectra of the solid hydrazones showed substantial absorption for the hydroxyl and >C=N-functions. The observation of the open-chain form only is not surprising, considering its predominance in solution (28). The 2,4-dinitrophenylhydrazones have ultraviolet absorptions identical to that of the 2,4-dinitrophenylhydrazone of the model compound 12 (one form only), further indicating the predominance of the open-chain form in solution.



11



$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_3-O-CH_2-CH_3$$

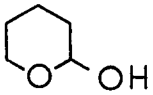
12

Ring-chain tautomeric equilibria are evident from the spectral properties of the hydroxyketones 6 and 8. The infrared spectrum of $5 \rightleftarrows 6$ has significant carbonyl and hydroxyl absorptions. Comparison of the intensity of the carbonyl band of 6 at $1721 cm^{-1}$, with that of the model compound 12 showed that there was 57.7 ± 0.5% of the open-chain form 6. This value is in good agreement with those obtained from NMR (57.6 ± 0.5%) and UV (57.3 ± 0.5%) determinations. The NMR spectra of the hydroxyketones showed two singlet methyl groups such that the sum of the integrations of these two peaks represented three protons. The percents of open-chain form in different solvents, calculated from the two resonances, are presented in Tables 1 and 2. The amount of open-chain ketone present in the equilibrium mixtures 5 $\rightleftharpoons$ 6 and 7 $\rightleftharpoons$ 8 in various solvents and solvent mixtures was calculated from the ultraviolet spectra, using compound 12 as a model for the open form. These results are presented in Tables 1, 2, 3, 4, 5 and 6.

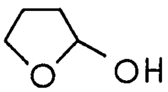
The effect of increased temperature (Figures 1 and 2) is to displace the equilibrium toward the open-chain tautomer. This is expected from entropy considerations, because of the greater degree of freedom in the open-chain form. This is substantiated by the rather large positive entropy value of about 6 to 10 eu in aqueous organic solvents, and by the smaller values of about 0.6 to 1.5 eu in pure organic solvents (Table 7). The relative change in enthalpy values for the series, however, was larger, $-\Delta H^{\circ} = 5$ to 9 kcal/mole for the aqueous organic solvents, and 0.7 to 1.0 kcal/mole for the pure organic solvents. Therefore enthalpy effects appear to contribute more in changing the position of the equilibrium. Similar temperature effects have been observed for oxazolidine-Schiff base (equation 4) (16), tetrahydro-2H-1,3,4-oxazolidine-hydroxyhydrazone (equation 5) (17), and 1-deoxyfructose equilibria, the last being closely analogous to 7 $\rightleftharpoons$ 8 (29). The proportion of open-chain 1-deoxyfructose was found by an NMR method to change from 1% at 25° to 5% at 45° and then to 25% at 85°. However, it was not established whether the ketone form was partially hydrated (9, 10); in the case of our ketones 6, 8, and 12, there was no evidence of hydration since the extinction coefficients in water were of the expected magnitude ($\epsilon = 24.6$).

The furanose forms of sugars are classically regarded as inherently less stable than the pyranose forms, and this has been explained by assuming that six-membered rings are more stable than five-membered. However, the difference in free energy of five- and six-membered rings is not pronounced because the flexible cyclopentane has greater entropy than the rigid cyclohexane. Replacement of a methylene group by an oxygen atom lessens the difference between the stability of the five- and six-membered ring systems by reducing the eclipsed interactions in the five-membered ring (12a).

From the data of Hurd and Saunders (8) the difference in free energy changes on cyclization between the two systems, tetrahydropyran-2-ol (<u>13</u>) and tetrahydrofuran-2-ol (<u>14</u>) in 75% aqueous dioxane at 25° is only 0.4 kcal/mole (12a).



<u>13</u>



<u>14</u>

Based on our equilibrium data in carbon tetrachloride, the difference in free energy changes on cyclization between 2-methyl-2-hydroxytetrahydropyran (<u>7</u>) and 2-methyl-2-hydroxytetrahydrofuran (<u>5</u>) is only 0.16 kcal/mole. This figure represents the difference in the stability between the two cyclic compounds. However, the difference in stability is not large; in fact, we found the reverse order of stability in dioxane-water (~0.95 mole fraction H_2O), the furanose form <u>5</u> was favored by 0.3 kcal/mole. Although there is a higher percent of the keto form <u>6</u> than <u>8</u> in the pure liquids, no valid comparison of the relative stabilities can be made since each compound is a different medium, and solvation may be different in each.

As might have been anticipated, solvent polarity also has a big effect on the equilibrium of hydroxyketones. The more polar the solvent, the greater is the tendency for the open-chain forms (<u>6</u> and <u>8</u>) which are evidently more polar than the ring forms. The qualitative effect of solvent polarity on the equilibrium of the open-chain and cyclic forms of $\underline{7} \rightleftharpoons \underline{8}$ can be seen in Figure 3 in which the percent ketone <u>8</u> is correlated with the Z values (30, 31) of the various solvents. Correlation of equilibrium constant with the dielectric constant of the solvent is much rougher, as can be seen by inspection of the results in Tables 1 and 2, in which solvents are arranged in order of increasing dielectric constant on going down the table.

The effect of aqueous-organic solvents are shown in Figures 4, 5 and 6. Figure 6 shows the very strong solvating ability of dimethylsulfoxide, and dimethylsulfoxide-water mixtures, especially where there is possibility for hydrogen bonding.

TABLE 1

Percent keto form 6 from NMR and UV methods[⌿]

Solvent	NMR method %6	δC[#]	δR[#]	UV method[$] %6	nm
pure liquid	54.5				
cyclohexane'	55.4			56.2	278
CCl_4	57.6	125	75	57.3	272
$CHCl_3$'	55.0			57.3	277
dioxane				54.5	275
acetone'	55.0				
ethanol'	54.8			55.7	274
methanol				55.4	273
acetonitrile'	55.0			56.0	276
DMSO'	61.0			64.0	278
water'	100			100	265
formamide	54.2				

[$] Spectra recorded at 25.1°

['] Deuterated solvents were used for NMR spectra.

[#] Chemical shifts of methyl groups, C= open-chain form and R= ring-form, in Hz downfield from external TMS standard.

[⌿] Results are reproducible within 1%.

TABLE 2

Percent keto form 8 from NMR and UV methods[†]

	NMR method			UV method[$]	
Solvent	%8	δC[#]	δR[#]	%8	nm
pure liquid	54.1	115	62		
cyclohexane'	51.4	106	56	53.5	280
CCl_4	51.2	122	70	51.0	272
$CHCl_3$'	54.0	130	77	55.1	275
dioxane				57.4	277
acetone'	54.8	107	55		
ethanol'	61.8	110	57	64.7	274
methanol				66.1	274
acetonitrile'	55.9	107	55	62.1	276
DMSO'	54.6	119	65	56.7	278
water'	100	130		100	278

[$] Spectra recorded at 25.1°

' Deuterated solvents were used for NMR spectra.

[#] Chemical shifts of methyl groups, C= open-chain form and R= ring-form, in Hz downfield from external TMS standard.

[†] Results are reproducible within 1%.

TABLE 3

Temperature effect on equilibrium data in various solvents'

	15°		25°		50°	
XA,B	C/R %	ln K	C/R %	ln K	C/R %	ln K
DA	53.9/46.1	0.156	54.5/45.5	0.181	57.2/42.8	0.290
DB	56.7/43.3	0.269	57.4/42.6	0.298	59.7/40.3	0.394
EA	54.1/45.9	0.164	55.7/44.3	0.228	57.3/42.7	0.294
EB	62.9/37.1	0.527	64.7/35.3	0.605	67.1/32.9	0.710
SA	62.8/37.2	0.524	64.0/36.0	0.575	67.1/32.9	0.710
SB	55.5/44.5	0.221	56.7/43.3	0.269	58.6/41.4	0.352
D_1A	88.4/11.6	2.03	92.0/8.0	2.44	95.5/4.5	3.06
D_2B	91.6/8.4	2.38	95.0/5.0	2.94	98.5/1.5	4.19
S_1A	95.6/4.4	3.08	97.2/2.8	3.55	99.0/1.0	4.59
S_2B	92.8/7.2	2.55	94.3/5.7	2.81	96.5/3.5	3.31

' Equilibrium data was obtained from ultraviolet spectra.

X = solvent

A = $\underline{5} \rightleftharpoons \underline{6}$

B = $\underline{7} \rightleftharpoons \underline{8}$

D = dioxane

E = ethanol

S = dimethylsulfoxide

D_1 = dioxane-water, 0.96 mole fraction H_2O

D_2 = dioxane-water, 0.95 mole fraction H_2O

S_1 = dimethylsulfoxide-water, 0.75 mole fraction H_2O

S_2 = dimethylsulfoxide-water, 0.70 mole fraction H_2O

TABLE 4

Percent keto forms in dioxane-water mixtures'

%6	χH_2O	%8	χH_2O
54.5	0	57.4	0
56.1	0.40	58.5	0.31
57.3	0.61	61.0	0.59
60.4	0.81	65.0	0.83
72.9	0.93	95.0	0.95
92.0	0.96	99.2	0.98
100	1	100	1

' Data obtained from ultraviolet spectra are reproducible within 1%.

TABLE 5

Percent keto forms in ethanol-water mixtures'

%6	$X\,H_2O$	%8	$X\,H_2O$
55.7	0	54.8	0
56.0	0.20	55.6	0.26
56.2	0.42	61.1	0.45
56.5	0.61	66.5	0.58
63.5	0.64	90.0	0.78
64.5	0.82	97.8	0.90
71.5	0.85	100	0.96
95.0	0.95	100	1
100	1		

' Data obtained from ultraviolet spectra are reproducible within 1%.

TABLE 6

Percent keto forms in DMSO-water mixtures'

%6	X_{H_2O}	%8	X_{H_2O}
64.0	0	61.0	0
67.5	0.16	66.0	0.10
77.0	0.36	72.5	0.21
87.5	0.52	87.7	0.42
92.5	0.61	100	0.58
100	0.72	100	0.76
100	0.97	100	1
100	1		

' Data obtained from ultraviolet spectra are reproducible within 1%.

TABLE 7

Thermodynamic calculations[a]

Solvent	$-\Delta H^o$ kcal/mole[b]	ΔS^o eu[c]
Equilibria of 5 $\rightleftharpoons$ 6		
dioxane-water[d]	5.5	6.7
DMSO-water[e]	8.1	9.9
dioxane	0.7	0.6
DMSO	1.0	1.5
ethanol	0.7	0.7
Equilibria of 7 $\rightleftharpoons$ 8		
dioxane-water[f]	9.3	9.2
DMSO-water[g]	4.8	7.2
dioxane	0.7	0.9
DMSO	0.8	0.8
ethanol	1.0	1.5

[a] Based on data in Table 3 and Figures 1 and 2 in which K and T were fitted to equation $\ln K = N(1/T) + C$.

[b] $\Delta H^o = -NR$, error approximately 5%.

[c] $\Delta S^o = CR$, error approximately 10%.

[d] 0.96 mole fraction water.

[e] 0.75 mole fraction water.

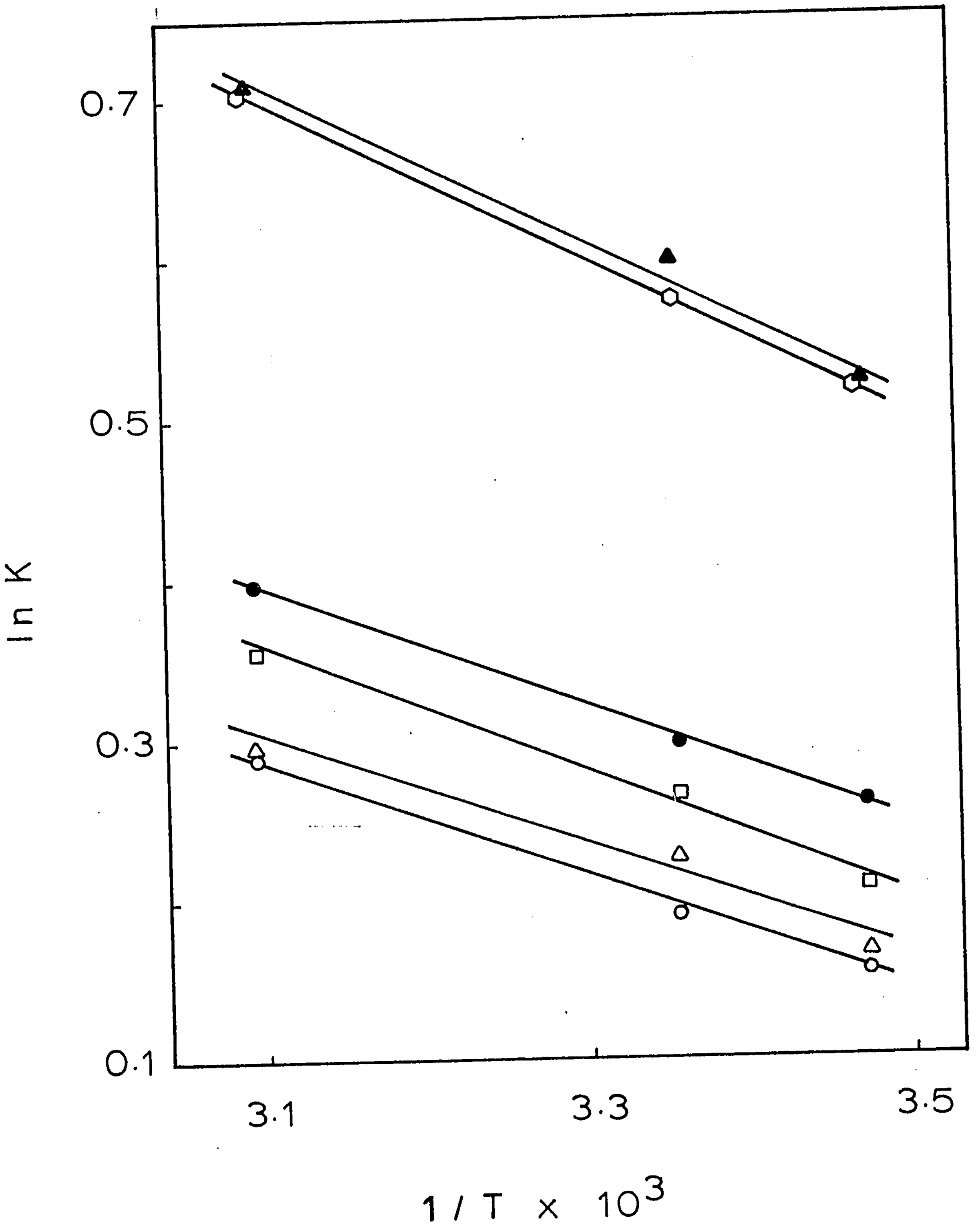
[f] 0.95 mole fraction water.

[g] 0.70 mole fraction water.

Figure 1

Temperature effect on equilibria in various solvents

○ 5 $\rightleftharpoons$ 6 in dioxane
● 7 $\rightleftharpoons$ 8 in dioxane
△ 5 $\rightleftharpoons$ 6 in ethanol
▲ 7 $\rightleftharpoons$ 8 in ethanol
⬡ 5 $\rightleftharpoons$ 6 in dimethylsulfoxide
□ 7 $\rightleftharpoons$ 8 in dimethylsulfoxide



0.7
0.5
ln K
0.3
0.1
3.1
3.3
3.5
1 / T x 10^3

Figure 2

Temperature effect on equilibria in various mixed solvents

⬡ 5 $\rightleftharpoons$ 6 in dioxane-water; 0.96 mole fraction H_2O

○ 7 $\rightleftharpoons$ 8 in dioxane-water; 0.95 mole fraction H_2O

△ 5 $\rightleftharpoons$ 6 in dimethylsulfoxide-water, 0.75 mole fraction H_2O

□ 7 $\rightleftharpoons$ 8 in dimethylsulfoxide-water, 0.70 mole fraction H_2O

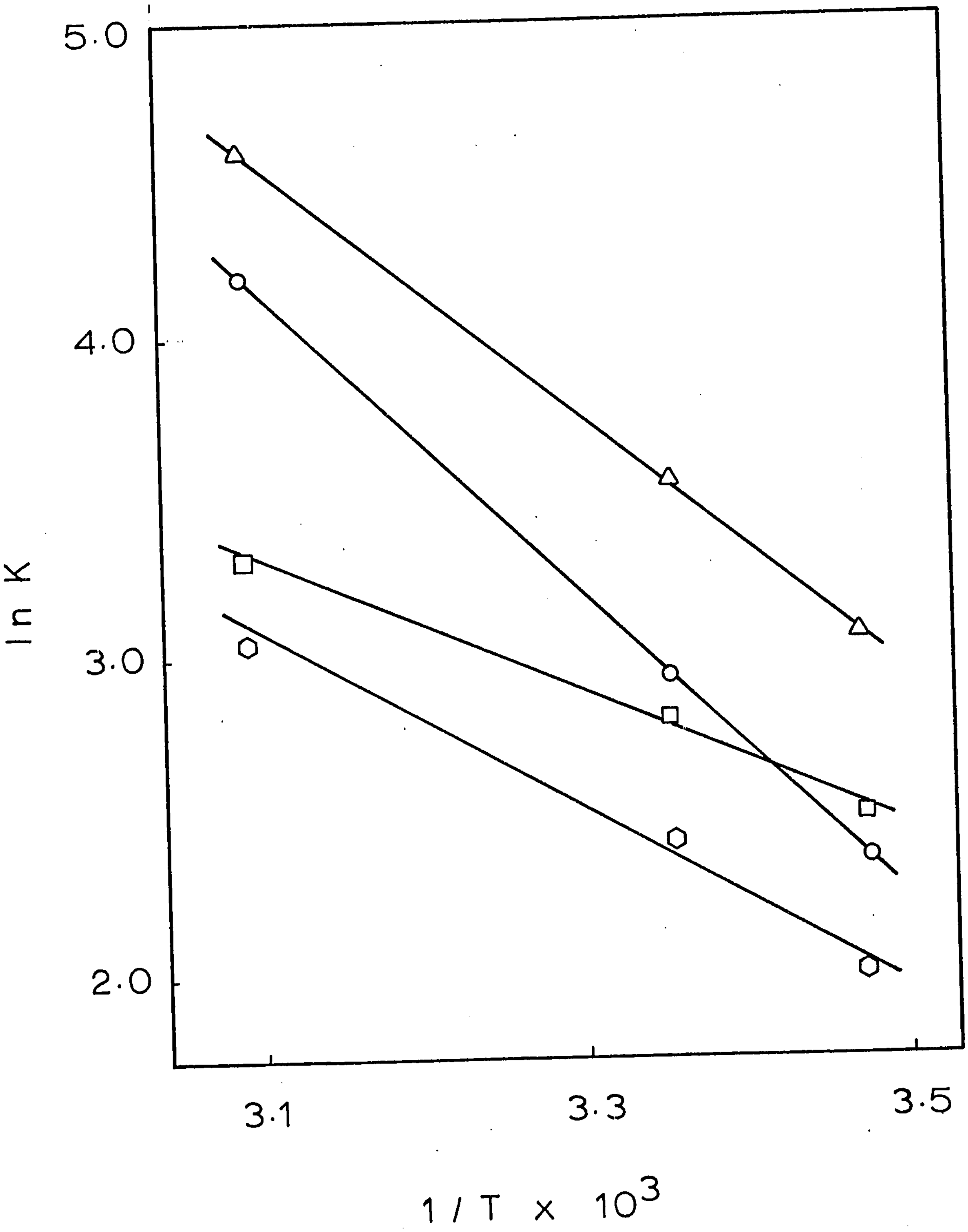

5.0
4.0
3.0
2.0
ln K
3.1
3.3
3.5
1 / T x 10^3

Figure 3

Effect of solvent polarity (Z) on the equilibrium $\underline{7} \rightleftharpoons \underline{8}$

	Solvent	Z value
○	H_2O	94.6
□	MeOH	83.6
△	EtOH	79.6
⬡	CH_3CN	71.3
●	DMSO	71.1
▲	$CHCl_3$	63.2

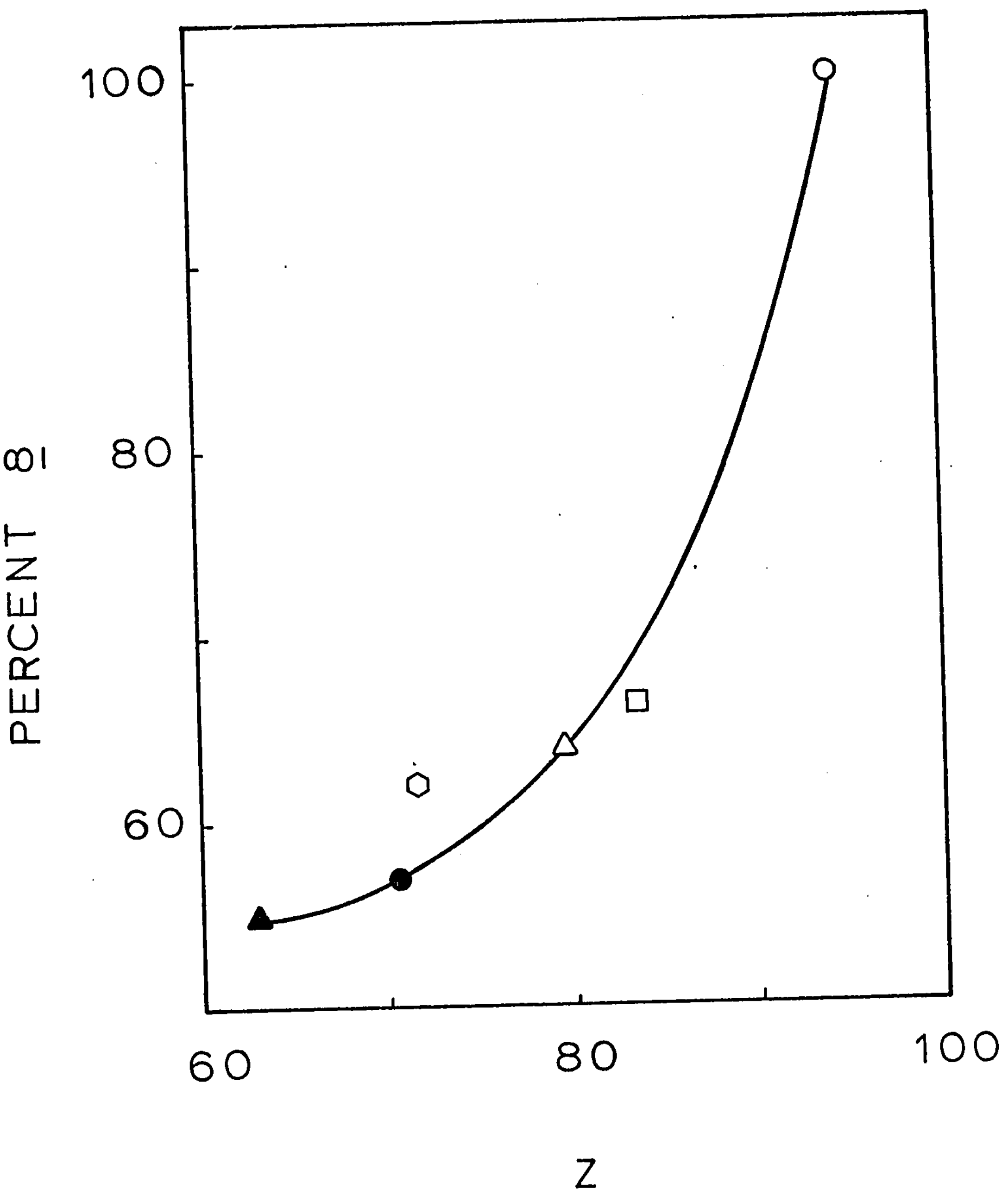

PERCENT $\underline{8}$
100
80
60
60
80
100
Z

Figure 4

Effect of mole fraction of water on equilibria in dioxane-water mixtures

△ $\underline{5} \rightleftharpoons \underline{6}$

○ $\underline{7} \rightleftharpoons \underline{8}$

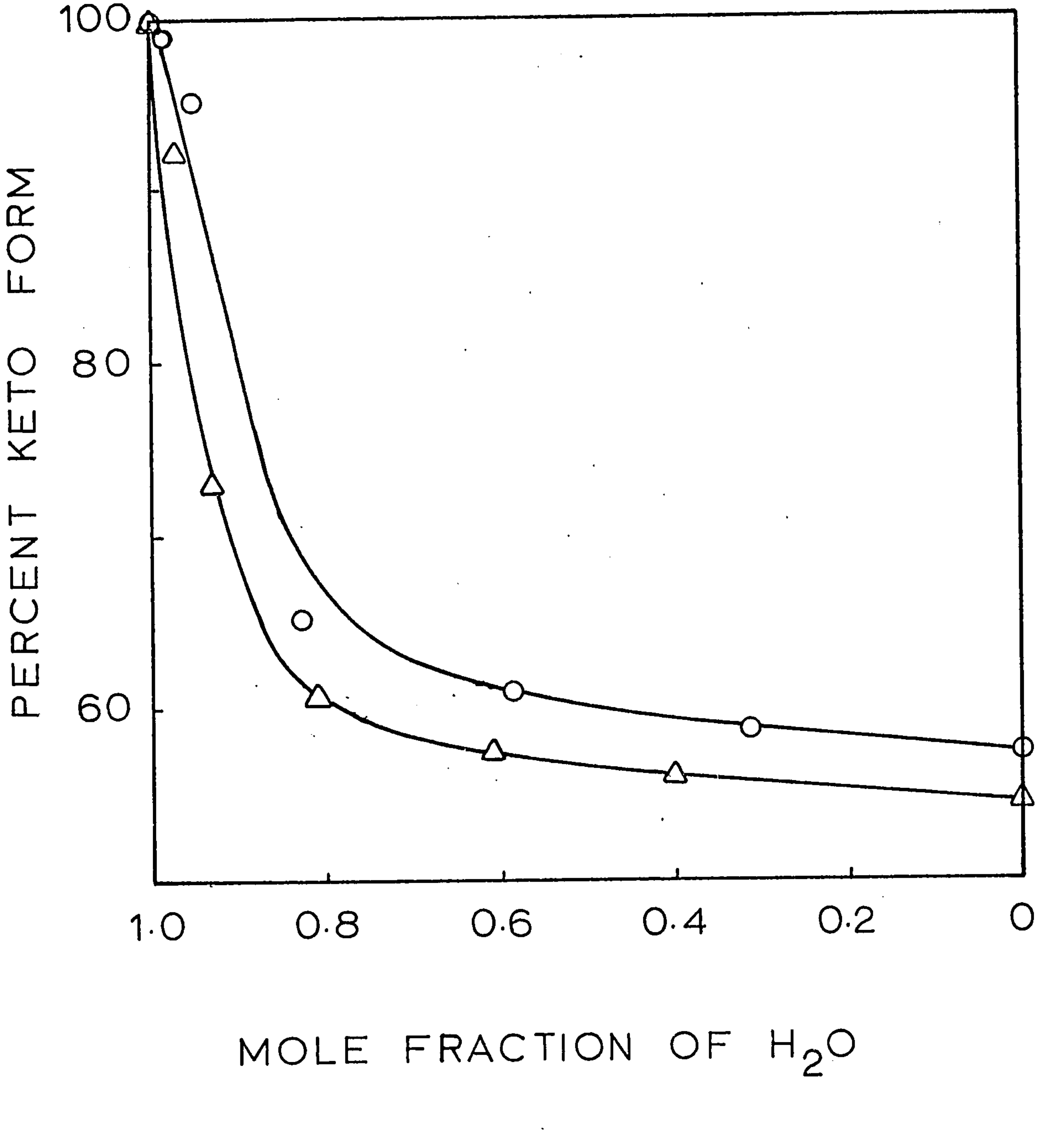
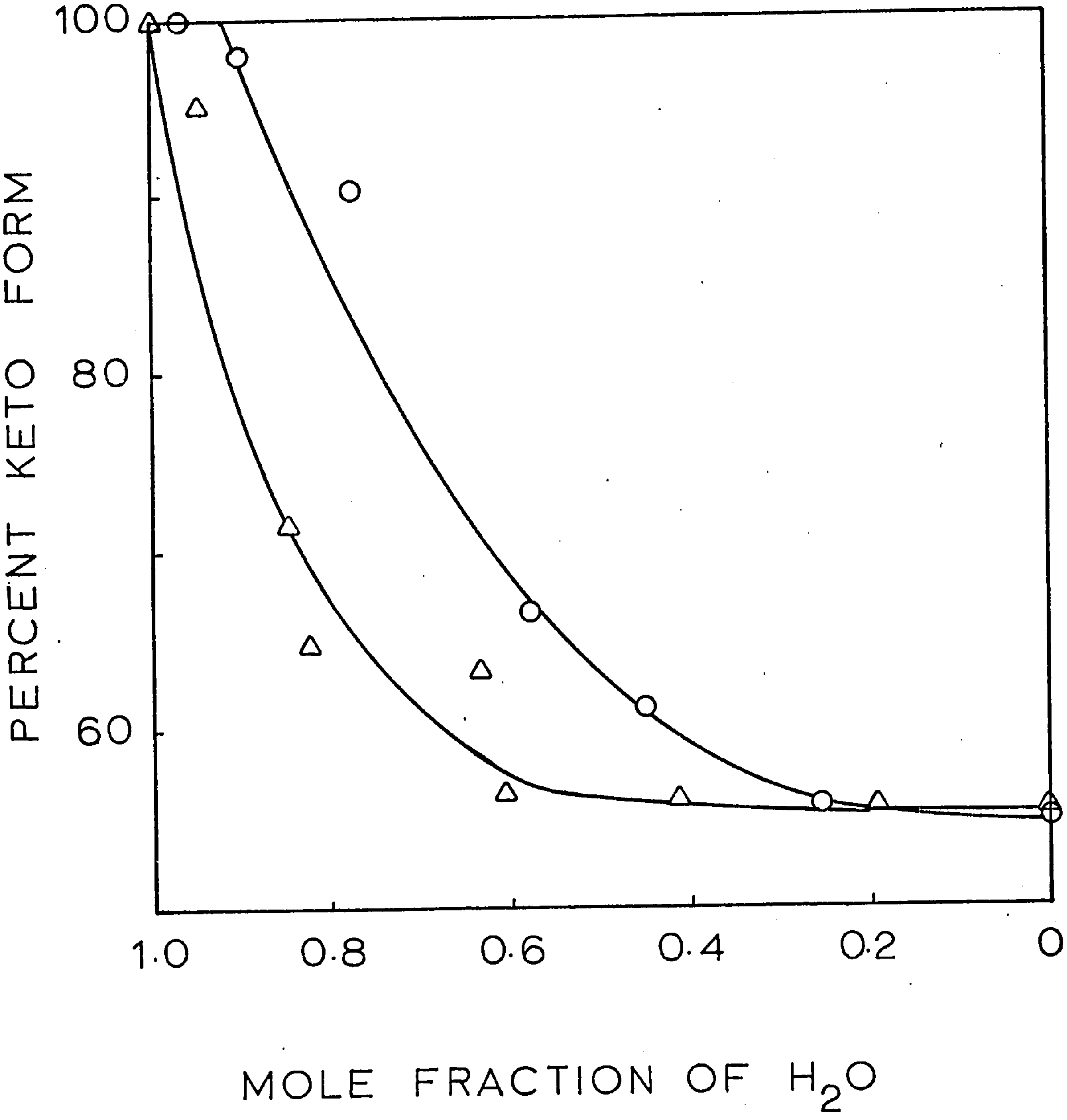

100
80
60
PERCENT KETO FORM
1·0
0·8
0·6
0·4
0·2
0
MOLE FRACTION OF H_2O

Figure 5

Effect of mole fraction of water on equilibria in ethanol-water mixtures

△ $\underline{5} \rightleftharpoons \underline{6}$

○ $\underline{7} \rightleftharpoons \underline{8}$



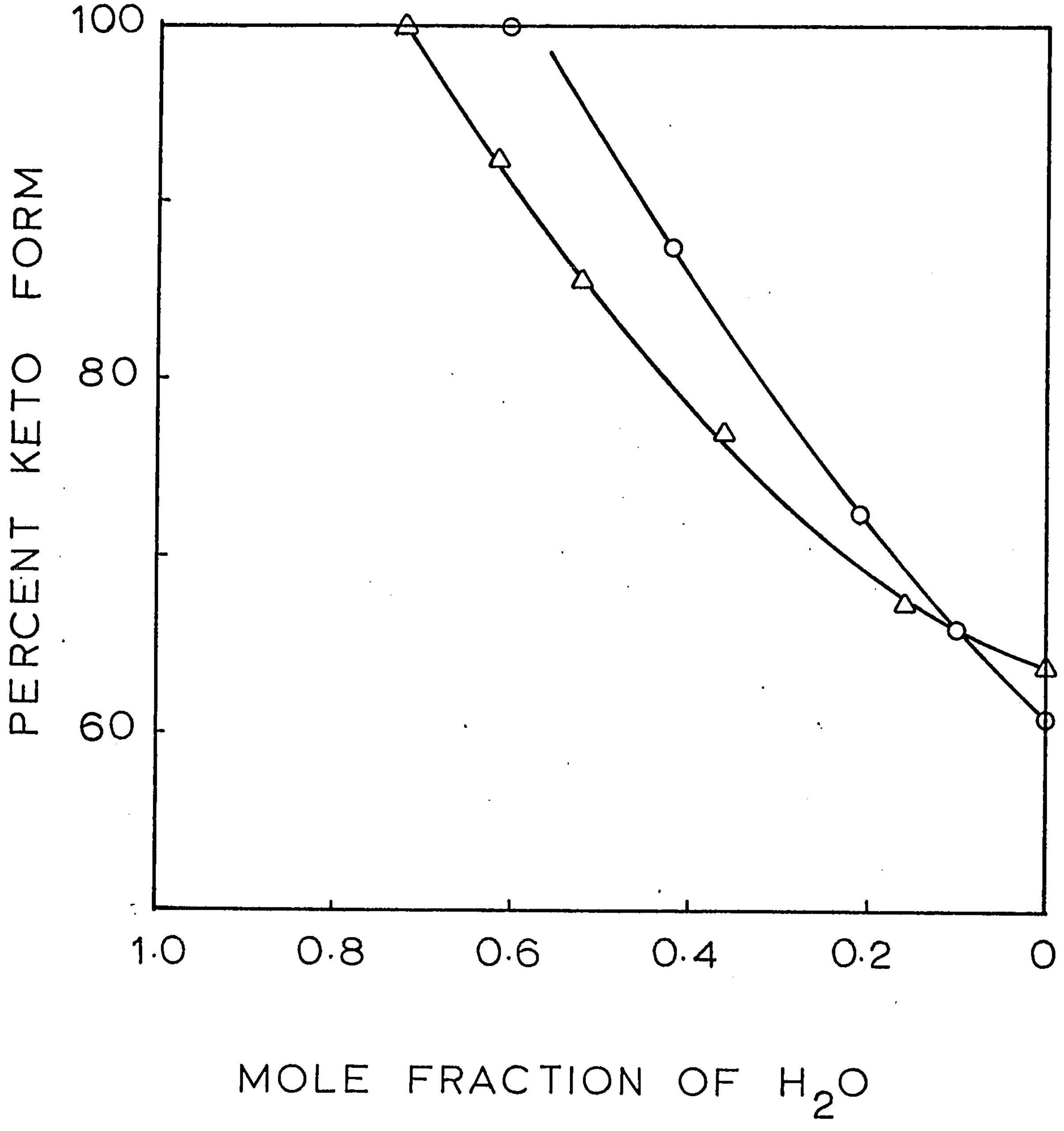
PERCENT KETO FORM
100
80
60
1.0
0.8
0.6
0.4
0.2
0
MOLE FRACTION OF H_2O

Figure 6

Effect of mole fraction of water on equilibria in DMSO-water mixtures

△ $\underline{5} \rightleftharpoons \underline{6}$

○ $\underline{7} \rightleftharpoons \underline{8}$


100
80
60
PERCENT KETO FORM
1.0
0.8
0.6
0.4
0.2
0
MOLE FRACTION OF H_2O

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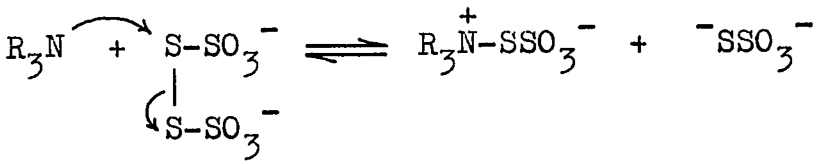
SUMMARY AND CONTRIBUTIONS TO KNOWLEDGE

1. The structures of the Tercinet products from the reaction of certain tertiary amines with silver sodium thiosulfate have been found not to be Bunte salts but rather N-ammonium-S-thiosulfates.

2. Tetrathionate ion was found to be the effective reagent in the Tercinet reaction. Maximum yields of N-ammonium-S-thiosulfates were obtained from the reaction of a number of tertiary amines with sodium tetrathionate. In this manner twelve compounds were synthesized and characterized. Four had previously been made by Tercinet, all the others were new compounds. The hydrolyses of these products have been studied in acidic and alkaline media.

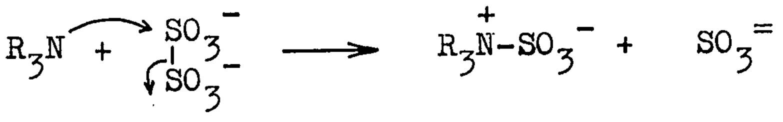
3. A mechanism has been proposed for this reaction, involving the nucleophilic attack of the tertiary amine on the divalent sulfur atom of tetrathionate ion, with elimination of thiosulfate ion.



$$R_3N + \begin{array}{c} S\text{-}SO_3^- \\ | \\ S\text{-}SO_3^- \end{array} \rightleftharpoons R_3\overset{+}{N}\text{-}SSO_3^- + {}^-SSO_3^-$$

This reaction is an equilibrium; however, further decompositions of the components have made a quantitative study impossible.

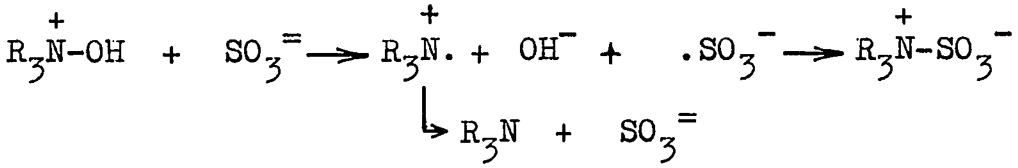
4. The sulfur trioxide complexes of certain tertiary amines can be formed by the reaction of the tertiary amine with sodium dithionate in boiling water.



$$R_3N + \begin{array}{c} SO_3^- \\ | \\ SO_3^- \end{array} \longrightarrow R_3\overset{+}{N}\text{-}SO_3^- + SO_3^{=}$$

In this manner seven ammonium-N-sulfonates (substituted sulfamic acids) have been prepared.

5. The reaction of strychnine N-oxide with aqueous sulfur dioxide is temperature dependent; the product is the sulfamic acid, strychninium-N_b-sulfonate, at 0°, but at 60° the product is strychnine and sulfate ion. The reaction has been found to proceed by a radical-ion mechanism by the use of the radical trap, hydroquinone.



$$R_3\overset{+}{N}\text{-}OH + SO_3^{=} \longrightarrow R_3\overset{+}{N}\cdot + OH^- + \cdot SO_3^- \longrightarrow R_3\overset{+}{N}\text{-}SO_3^-$$

$$\hookrightarrow R_3N + SO_3^{=}$$

6. The sulfitoamine, (N_b-strychninio) sulfite, was prepared by the reaction of strychnine N-oxide with sulfur dioxide in anhydrous benzene. Although it rearranges to strychninium-N_b-sulfonate by a radical-ion mechanism, the rearrangement is too slow for the sulfitoamine to be an intermediate in the conversion of the amine oxide to the sulfamic acid in the reaction of strychnine N-oxide with sulfur dioxide in water at 0°.

7. The reactions of N,N-dimethylaniline N-oxide and N,N-diethyl aniline N-oxide with aqueous sulfur dioxide, and the hydrolysis of the sulfitoamine, (N,N-dimethylanilinio) sulfite, have been found to proceed by radical-ion mechanisms by the trapping technique.

8. By investigation of the reaction of N,N-dimethylbenzylamine N-oxide with aqueous sulfur dioxide, it was found that the reaction followed two pathways, deoxygenation to N,N-dime-

thylbenzylamine (35%), and dealkylation to N-methylbenzylamine (8%) and an aminosulfonic acid (52%), which hydrolyzed quantitatively to benzaldehyde and dimethylamine. This reaction was unaffected by the addition of radical traps and no evidence for radical intermediates was found by physical methods.

9. The reaction of β-phenylhydroxylamine with aqueous sulfur dioxide was found to be more complex than had been reported. Metanilic acid was found, in addition to the aniline, orthanilic acid, sulfanilic acid, and phenylsulfamic acid already reported. There was no evidence for radical intermediates.

10. The sulfatoamines, (N_b-strychninio) sulfate and (N,N-dimethylanilinio) sulfate, were prepared by the reaction of the corresponding amine oxides with pyridine-sulfur trioxide complex. Both sulfatoamines were hydrolyzed to corresponding amine oxide and sulfate ion in dilute acid or alkali.

11. It has been substantiated by ultraviolet, infrared, and nuclear magnetic resonance studies that 5-hydroxy-2-pentanone and 6-hydroxy-2-hexanone are in mobile tautomeric equilibrium with their cyclic forms, 2-methyl-2-hydroxytetrahydrofuran and 2-methyl-2-hydroxytetrahydropyran respectively.

12. In most organic solvents there is a slight preference for the open-chain form of the hydroxyketone over the cyclic hemiketal. Highly polar organic solvents or organic solvent-water mixtures favor the open-chain tautomer and in pure water there was no evidence of any cyclic form whatever. The percent open-chain form shows a better correlation with the Z values rather than with the dielectric constants of the various solvents.

13. Increase in temperature displaces the equilibrium toward the open-chain tautomer. Entropy considerations favor the open-chain form by about 6 to 10 eu (±10%) in aqueous-organic solvents and by about 0.6 to 1.5 eu (±10%) in pure organic solvents. However, the relative change in enthalpy values was larger, about 5 to 9 kcal/mole (±5%) for the aqueous-organic solvents, and about 0.7 to 1.0 kcal/mole (±5%) for the pure organic solvents.

APPENDIX

INFRARED SPECTRA OF N-O, N-S, AND S-O BONDS

Although many of the infrared absorption bands of complex organic compounds cannot be assigned accurately, comparisons with a wide range of known spectra can provide a wealth of structural information about a molecule.

N-S Stretching Frequencies

Empirical correlations show that the nature of S-O bonding and S-N bonding is analogous and that a linear relationship exists between the bond lengths and the wavelengths of the absorption bands of S-N bonds. Since bond orders up to three may occur, a considerable range of frequencies is observed (630-1690cm^{-1}), the frequency increases with increasing order (1). For compounds that contain a formal S-N single bond, the experimentally determined bond distance varies over the range 1.58-1.79 Å (1). Small variations in the bond distance are to be expected as a result of variations in the character of the orbitals used, and in the sulfur valence state, as well as in the nature of the groups attached to sulfur and nitrogen. However, these factors are insufficient to account for the magnitude of the observed variations, and these may be due to some π character in the bond as a result of pπ-dπ overlap involving the lone pair on nitrogen and the empty 3d orbitals of sulfur.

Sulfamic acid exists as the zwitterion $H_3\overset{+}{N}-SO_3^-$ (2), so that the nitrogen lone pair is unavailable for donation to the 3d orbitals of sulfur. The S-N bond length is 1.73 Å (2), suggesting little or no pπ-dπ overlap. Thus, the S-N bond is essentially restricted to the 2σ electrons only and the observed stretching frequency of 688cm^{-1} (1,2) may be taken as being close to that expected for a single S-N bond.

For other compounds containing S-N single bonds, sulfamate ion (H_2N-SO_3^-) 780cm^{-1} (1), sulfonamides (R-SO_2-NR_2) 800-920cm^{-1} (1), sulfamides (R_2N-SO_2-NR_2) 900-930cm^{-1} (1), and sulfenamides (R-S-NR_2) 900-1000cm^{-1} (3), the observed stretching frequency is higher than in sulfamic acid; since the lone pair of nitrogen is available, the extent of pπ-dπ overlap is increased, and consequently, the S-N stretching frequency increases. The stretching frequency of the S-N bond of thionitrites (R-S-N=O) has been empirically assigned to the region 630-660cm^{-1} (4); evidently the -N=O group is election-withdrawing; and thus, the S-N stretching frequency is decreased. The compounds containing an S-N bond prepared in Chapters 1, 2, 3 and 4 have S-N stretching frequencies closer to the value for sulfamic acid, since the lone pair on nitrogen in these compounds is not available (Table 1).

TABLE 1

S-N Stretching frequencies of some compounds

Compound	ν S-Ncm^{-1}
sulfamic acid	688 (ref 1,682)
pyridine. SO_3	690
strychninium-N_b-sulfonate	700
N_b-strychninium-S-thiosulfate	705
N,N-dimethylanilinium sulfonate	690

N-O Stretching Frequencies

Aliphatic amine oxides ($R_3\overset{+}{N}-O^-$) absorb strongly in the region 970-950cm^{-1} (5), the aromatic amine oxides (such as pyridine N-oxide) at 1320-1200cm^{-1} (6a) due to the N-O stretching frequency. Oae and coworkers have assigned the band at 960cm^{-1} to the N-O stretching frequency of N,N-dimethylaniline N-oxide (7). The N-O stretching frequency of $H_3\overset{+}{N}-O-SO_3^-$ and of $(CH_3)_3\overset{+}{N}-O-SO_3^-$ occurs at approximately 1000cm^{-1} (8). The assignments of the N-O stretching frequencies of the compounds prepared in Chapters 3 and 5 are given in Table 2.

TABLE 2

N-O Stretching frequencies of some compounds

Compound	ν N-Ocm^{-1}
strychnine N-oxide	958
N,N-dimethylaniline N-oxide	965
(N_b-strychninio) sulfite	990
(N,N-dimethylanilinio) sulfite	1010
(N_b-strychninio) sulfate	1000
(N,N-dimethylanilinio) sulfate	1000

S-O Frequencies

For sulfur-oxygen bonding there is a direct relationship of bond lengths and bond strengths with the absorption frequency. There is also a correlation of the substituents on sulfur or oxygen with the symmetric and asymmetric stretching modes of $-SO_2-$ and $-SO_3-$ groups (9,10). Electronegative substituents tend to shift the stretching frequencies to higher wave numbers (Table 3).

TABLE 3

SO_2 and SO_3 Stretching frequencies in cm^{-1}

Compound	$\nu_{asym}SO_2$ or SO_3	$\nu_{sym}SO_2$ or SO_3
$R-SO_2-R$ (9)	1340-1310	1140-1130
$R-SO_2-SR$ (9)	1365-1335	1154-1144
$R-SO_2-OR$ (9)	1420-1330	1200-1145
$R-SO_2-NH_2$ (9)	1370-1330	1160-1120
$RO-SO_2-OR$ (9)	1440-1350	1230-1150
$R-SO_2-Cl$ (9)	1370-1365	1190-1170
$R-SO_2-F$ (9)	1412	1205
$R-SO_3H$(anhyd) (9)	1355-1342	1170-1150
hydrate or salt (9)	1260-1150	1080-1010
$H_3\overset{+}{N}-SO_3^-$ (2)	1310	1066
$H_2N-SO_3^-$ (1)	1202	1059
$H_3\overset{+}{N}-O-SO_3^-$ (8)	1340	1062
$H_3C-O-SO_3^-$ (11)	1221	1063
$R-S-SO_3^-$ (12)	1250-1190	1050-1040
$SO_4^=$ (6b)	1130-1080	1010-980(usually IR inactive)
$^-S-SO_3^-$ (9)	1130-1070	1000-960
$HO-SO_3^-$ (6b)	1190-1160	1080-1015
$S_2O_6^=$ (10)	1235-1206	1090-1000

From the data in Table 3, probable assignments were made of the SO_2 and SO_3 stretching frequencies observed in the spectra of the compounds prepared in Chapters 1, 2, 3, 4 and 5 (Table 4).

TABLE 4

SO_2 and SO_3 Stretching frequencies in cm^{-1}

Compound	$\nu_{asym}SO_2$ or SO_3	$\nu_{sym}SO_2$ or SO_3
pyridine.SO_3	1300	1060
N,N-dimethylanilinium sulfonate	1240	1000
strychninium-N_b-sulfonate	1250	1000
N_b-strychninium-S-thiosulfate	1250	1020
(N,N/dimethylanilinio) sulfite	1320	1060
(N_b-strychninio) sulfite	1315	1060
(N,N-dimethylanilinio) sulfate	1340	1110
(N_b-strychninio) sulfate	1335	1120
N,N-dimethylamino-o-benzenesulfonic acid	1245	1080
N,N-dimethylamino-p-benzenesulfonic acid	1210	1120

The SO_3 deformation frequencies (also called S-O stretch) are somewhat characteristic of the compound. However, not too much information on these modes is available in the literature; a few that are reported are given in Table 5.

TABLE 5

SO_3 Deformation frequencies in cm^{-1}

Compound	δSO_3
sulfonic acids (6b)	700-600
$R-S-SO_3^-$ (12)	600-640
$H_3\overset{+}{N}-O-SO_3^-$ (8)	705
$H_3\overset{+}{N}-SO_3^-$ (2)	534
$H_3C-O-SO_3^-$ (11)	755
$SO_4^=$ (13)	640-610
$^-S-SO_3^-$ (13)	690-660 and 550-530

From the data in Table 5, probable assignments of SO_3 deformation modes were made for the compounds in Chapters 1, 2, 3, 4 and 5 (Table 6).

Miscellaneous Frequencies

The *ortho* - and *para* - sulfonic acids of aniline and N,N-dimethylaniline of Chapters 3 and 4, have characteristic ring deformation modes at 765cm^{-1} for *ortho* substituted benzene, and at 832cm^{-1} for *para* substituted benzene. The ring deformation patters for N,N-dimethylaniline, its N-oxide, and the N-oxide complexes, and the SO_3 adduct of the amine, are those characteristic of monosubstituted benzenes, two bands at 750 and 690cm^{-1}.

The infrared spectra of the N-ammonium-S-thiosulfates prepared in Chapter 1 showed that they were not merely the thiosulfate salts of the various amines. The thiosulfate salt of strychnine prepared independently had strong broad absorptions between 2650 and 2400 cm^{-1} characteristic of the N-H stretching frequency of a tertiary amine salt (6c) whereas N_b-strychninium-S-thiosulfate did not have these strong absorptions. The thiosulfate salt had bands at 1150 (ν_{asym} SO_3), 990 ($\nu_{sym}SO_3$), 750 and 550cm^{-1} (δSO_3).

TABLE 6

SO_3Deformation frequencies in cm^{-1}

Compound	δ SO_3
pyridine.SO_3	590,560
N,N-dimethylanilinium sulfonate	575
strychninium-N_b-sulfonate	575
N_b-strychninium-S-thiosulfate	610
(N,N-dimethylanilinio) sulfite	580
(N_b-strychninio) sulfite	590
(N,N-dimethylanilinio) sulfate	615
(N_b-strychninio) sulfate	622
N-N-dimethylamino-o-benzenesulfonic acid	620,570
N,N-dimethylamino-p-benzenesulfonic acid	670,570

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