# *N*-Ammonium-*S*-thiosulfate zwitterions from alkaloids and tertiary amines

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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.

Les composés préparés par Tercinet (1) par la réaction de différentes alcaloïdes 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 alcaloïdes avec la tetrathionate de soude.

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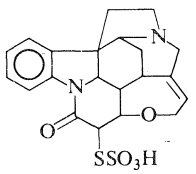
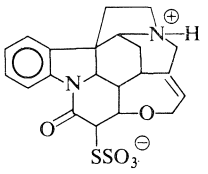
In 1944 André Tercinet (1) described the reaction of silver sodium thiosulfate ($Ag_2S_2O_3$.-$2Na_2S_2O_3$) with strychnine, brucine, quinine, and harmine to give crystalline solids. He formulated these compounds as *S*-thiosulfate esters, the compound from strychnine, for example, being assigned the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




**1**




**2**

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).

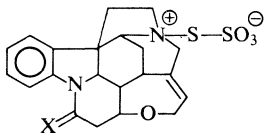
We were led to reinvestigate Tercinet's reaction because of the great usefulness of Bunte salts in synthesis (5), and because of the potential use of such compounds as anti-radiation agents (6, 7). However, while we obtained products having the composition and physical properties reported by Tercinet, 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 thiosulphate ion ($^{\ominus}S—SO_3^{\ominus}$) to tetrathionate ion ($^{\ominus}O_3S—S—S—SO_3^{\ominus}$), presumably via the radical $\cdot S—SO_3^{\ominus}$ (8*a*), 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 6 *N* hydrochloric acid yields strychnine, sulfur, and sulfate ion in essentially quantitative yields. All

[1]Née Josephine Jaworska, holder of NRCC Studentship, 1967–1969.



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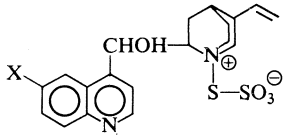

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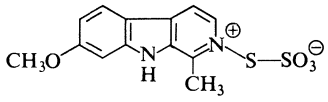


5

of this evidence points to a linkage of the $S—SO_3^{\ominus}$ group to nitrogen and not to carbon, since an N—S linkage can be broken by hydrolysis (11), so that the acid-catalyzed hydrolysis is represented by eq. [1].

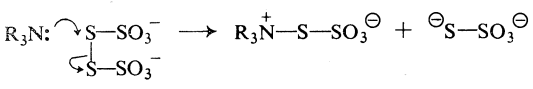
$$[1] \quad R_3\overset{+}{N}—S—SO_3^- + H_2O \rightarrow R_3N + S + H_2SO_4$$

Bunte salts are hydrolyzed by alkali to mixtures of sulfite ion, disulfides, sulfinates, and other products (5). 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". This also points to the presence of a hydrolyzable $\diagdown\overset{+}{N}—S—SO_3^-\diagup$ group.

The facile recovery of the strychnine by acid or alkaline treatment of Tercinet's product could be explained if the latter were merely the thiosulfate salt of strychnine ($C_{21}N_{24}N_2O_5S_2$). 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 5).

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. 12) 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 $pK_a \simeq 7.4$ (15), and it seems likely that the *N*-ammonium-*S*-thiosulfate structure is formed by a reaction, as shown in eq. [2], for

[2]



which their amino centers are insufficiently nucleophilic.[2] Reaction [2] has parallels in the reactions of several other nucleophiles (e.g. thiosulfate (13), cyanide (8*b*), azide (8*b*)) with tetrathionate ion.

On grounds of nucleophilicity, it might be expected that strychnidine would react at its more basic amino center (12) with tetrathionate to give the compound **3** (X = $H_2$). This was confirmed by its ultraviolet (u.v.) spectrum (Table 1), 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 (14).

The question of reaction site also arises with respect to Tercinet's product $C_{20}H_{24}N_2O_5S_2$ from quinine, and to the similar derivatives obtained from cinchonine and cinchonidine.[3] Again, these compounds are hydrolyzed by acid

[2]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.

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

TABLE 1

Ultraviolet spectra in ethanolic solution

| Compound | $\lambda\lambda_{max}$(nm) and $\varepsilon\varepsilon$* |
|---|---|
| Strychnine | 254(17 800), 280(6 100), 288(4 810) |
| **3**, X = O | 254(17 800), 280(6 100), 288(4 800) |
| Strychnidine | 254(17 700), 303(2 500), |
| **3**, X = $H_2$ | 254(17 700), 303(2 500), |
| Brucine | 254(17 800), 280(6 100), 288(4 800) |
| $N_b$-Brucinium-*S*-thiosulfate | 254(17 800), 280(6 100), 288(4 800) |
| Quinine | 232(74 400), 279(8 740), 332(11 100) |
| **4**, X = $OCH_3$ | 232(74 400), 279(8 750), 332(11 100) |
| Cinchonine | 227(47 000), 284(7 790), 314(4 850) |
| **4**, X = H | 227(47 000), 284(7 790), 314(4 860) |
| Harmine | 242(24 100), 307(10 200), |
| Harmine hydrochloride | 249(18 000), 325(10 600), |
| **5** | 249(18 000), 325(10 600), |
| 6-Methyoxyquinoline | 229(27 000), 269(2 830), 327(4 000) |
| 6-Methoxyquinoline hydrochloride | 250(27 700), 312(4 100), 340(4 100) |
| **7**, X = $OCH_3$ | 250(27 700), 312(4 100), 340(4 100) |
| 2-Phenyl[1,2-*a*]imidazopyridine | 245(34 500), 322(8 830) |
| 2-Phenyl[1,2-*a*]imidazopyridine hydrochloride | 239(20 700), 303(15 200) |
| **8** | 239(20 700), 303(15 200) |

*In parentheses.

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 $\cdot S—SO_3^{\ominus}$ to the more basic quinuclidine nitrogen, as shown in **4** (X = H or OMe) would be expected and is indicated by the u.v. 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 1. In addition, the nuclear magnetic resonance (n.m.r.) 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 2 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 n.m.r. spectrum of the

TABLE 2

Selected n.m.r. signals

| Compound in DMSO-$d_6$ | Signals (δ, p.p.m.) |
|---|---|
| Cinchonine | 7.6–8.9 (m, 6H)* |
| **4**, X = H | 7.6–8.9 (m, 6H)* |
| Quinine | 7.75–9.1 (m, 5H)* |
| **4**, X = OMe | 7.75–9.1 (m, 5H)* |
| Harmine | 6.7–7.1 (m, 2H), 7.7–8.25 (m, 3H), 7.3 (s, 1H)† |
| Harmine·$CF_3CO_2H$ | 6.8–7.15 (m, 2H), 8.2–8.55 (m, 3H), 12.3 (s, 1H)† |
| **5** | 6.9–7.2 (m, 2H), 8.2–8.55 (m, 3H), 12.3 (s, 1H)† |
| 6-Methoxyquinoline§ | 8.71‡ (d of d, 1H), 7.9–8.1 (two d, 2H) |
| 6-Methoxyquinoline·$CF_3CO_2H$ | 9.14‡ (d of d, 1H), 8.7–8.9 (two d, 2H) |
| **7**, X = OMe | 9.14‡ (d of d, 1H), 8.7–8.9 (two d, 2H) |
| 2-Phenyl(1,2-*a*)imidazopyridine | 8.30 (s, 1H), 8.38 (d, 1H) |
| 2-Phenyl(1,2-*a*)imidazopyridine ·$CF_3CO_2H$ | 8.55 (s, 1H), 8.78 (d, 1H) |
| **8** | 8.55 (s, 1H), 8.78 (d, 1H) |

*Aromatic H.
†Indole NH.
‡Proton at 2-position (22); $J_{2,3}$ = 5 c.p.s.; $J_{2,4}$ = 1.5 c.p.s.
§Solvent: $CDCl_3$.

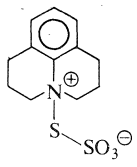
TABLE 3

Infrared peaks ($cm^{-1}$) of *N*-ammonium-*S*-thiosulfate derivatives in KBr

| Parent amine | $\nu_{asym}(SO_3)$ | $\nu_{sym}(SO_3)$ | $\nu$(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 | 1250 | 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 |

product (Table 2) shows a deshielding 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 u.v. spectrum of the product resembled very closely the spectrum of the hydrochloride of harmine (Table 1). 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 (15).

If the Tercinet products are formed by the action of tetrathionate according to equation 2, it might be expected that products having the grouping $-\overset{\oplus}{N}-S-SO_3^{\ominus}$ 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 (16) 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: juolidine (**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 (i.r.) spectra, recorded in Table 3.[4] The structure **7** (X = $OCH_3$) for the product from 6-methoxyquinoline is in accord with its u.v. (Table 1) and n.m.r. (Table 2) spectra, both of which indicate quaternization of the ring nitrogen.



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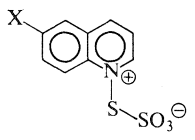

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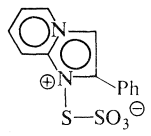

**8**

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 eq. [2] 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 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

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

TABLE 4
Physical properties of *N*-ammonium-*S*-thiosulfates

| Parent amine | Melting point °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).

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 p*H* of the solution remains near neutrality throughout the reaction.

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]

## Experimental

The i.r. spectra were recorded with a Perkin–Elmer Model 337 spectrophotometer, n.m.r. spectra with a Varian A-60 spectrophotometer, and u.v. 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 (17), dihydrostrychnine (18), and neostrychnine (19) were prepared by methods in the literature, and had the correct physical constants; the other alkaloids and bases were commercial products, and were used without purification. Sodium tetrathionate was made according to Partington's method (20) 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.

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

*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 h, 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° decomposition (lit. 245° decomposition (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 h; 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° decomposition. Addition of a small amount of acetic acid reduced the reaction time to 1½ h, but the yield was only 75%. Excess acetic acid lowered the reaction time to 15 min, 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 4. 6-Methoxyquinoline, quinoline, and juolidine were used in

TABLE 5

Analyses of *N*-ammonium-*S*-thiosulfates

| Parent amine | Product empirical formula | Analyses Calcd.% Found% C | H | N | S | Molecular weight* |
|---|---|---|---|---|---|---|
| Strychnine | $C_{21}H_{22}N_2O_5S_2$ | 56.48 | 4.96 | 6.27 | 14.36 | 446.5 |
| | | 56.41 | 4.90 | 6.31 | 14.45 | 440±10 (EtOH, $H_2O$, MeOH) |
| Brucine | $C_{23}H_{26}N_2O_7S_2$ | 54.75 | 5.19 | 5.55 | 12.71 | 504.5 |
| | | 55.00 | 5.28 | 5.43 | 12.81 | 505±10 (EtOH) |
| Harmine | $C_{13}H_{12}N_2O_4S_2$ | 48.14 | 3.76 | 8.64 | 19.77 | 324.3 |
| | | 48.33 | 3.86 | 8.88 | 20.01 | 320±10 (MeOH) |
| Quinine | $C_{19}H_{24}N_2O_5S_2$ | 55.03 | 5.54 | 6.42 | 14.69 | 436.5 |
| | | 55.05 | 5.52 | 6.32 | 14.48 | 425±10 ($H_2O$) |
| Cinchonine | $C_{18}H_{22}N_2O_4S_2$ | 56.14 | 5.45 | 6.89 | 15.76 | 406.5 |
| | | 56.30 | 5.36 | 6.93 | 15.83 | 395±10 (MeOH) |
| Cinchonidine | $C_{18}H_{22}N_2O_4S_2$ | 56.14 | 5.45 | 6.89 | 15.76 | 406.5 |
| | | 56.25 | 5.57 | 6.78 | 15.90 | |
| 6-Methoxy-quinoline | $C_{10}H_9NO_4S_2$ | 44.29 | 3.35 | 5.17 | 23.60 | 271.1 |
| | | 44.39 | 3.60 | 5.31 | 23.34 | 270±10 ($H_2O$) |
| Quinoline | $C_9H_7NO_3S$ | 44.82 | 2.93 | 5.81 | 26.54 | 241.1 |
| | | 44.70 | 2.95 | 5.69 | 26.64 | 240±10 (MeOH) |
| Juolidine | $C_{12}H_5NO_3S$ | 50.52 | 5.30 | 4.91 | 22.43 | 285.2 |
| | | 50.39 | 5.28 | 4.77 | 22.56 | 285±10 ($H_2O$) |
| 2-Phenyl[1,2-*a*] imidazopyridine | $C_{12}H_{10}N_2O_3S$ | 50.98 | 3.29 | 9.15 | 20.89 | 306.2 |
| | | 50.69 | 3.57 | 8.93 | 20.64 | 300±10 (EtOH) |
| Strychnidine | $C_{21}H_{24}N_2O_4S_2$ | 55.99 | 5.82 | 6.22 | 14.20 | 432.4 |
| | | 55.89 | 5.67 | 6.48 | 14.38 | |
| Dihydrostrychnine | $C_{21}H_{24}N_2O_5S_2$ | 56.24 | 5.39 | 6.25 | 14.28 | 448.5 |
| | | 56.29 | 5.41 | 6.50 | 14.49 | |

*By vapor pressure osmometry in the solvents indicated.

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 ($\nu_{max}$(KBr) 1230, 1035, 690, 610 $cm^{-1}$) which had a bad combustion analysis.

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

$N_b$-Strychninium-*S*-thiosulfate (2.63 g) was stirred at room temperature for a few min with 6 *N* hydrochloric acid (50 ml). The yellow solution was extracted 4 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 i.r. absorption between 4000 and 400 $cm^{-1}$, u.v. absorption at 264 mμ in ethanol (log ε 3.0) with a shoulder at 275 mμ (21). 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° decomposition (lit. 286–288° decomposition), by an i.r. 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 (1.578 g, 3.537 mequiv.) was exactly neutralized by addition of sodium hydroxide (22.15 ml, 0.1597 *N*, 3.535 mequiv.). A white precipitate of strychnine (1.18 g, 3.533 mequiv., m.p. 286–288° decomposition) identified by i.r. 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 warm 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 h. 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 $7.9 \times 10^{-4}$ *M*, and of **3** (X = O), $1.5 \times 10^{-2}$ *M*, so that both compounds were present in the first experiment above in amounts greater than required for saturation.

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