the salicylic radical may scarcely be considered a serious objection.

SUMMARY

Alcoholic solutions of local anesthetic bases derived from *p*-aminobenzoic acid show strong absorption of ultraviolet light in the wave-length band 2700 to 3200 Å.

The somewhat water-soluble salicylates show similar phenomena with slightly improved "filter" characteristics. Acetylsalicylic and salicylsalicylic salts showed no obvious advantages over the salicylates.

One per cent aqueous preparations of Larocaine salicylate gave good results in actual trials as "sunscreens" and it is concluded that most surface anesthetics of this type offer interesting possibilities in the formulation of such preparations.

REFERENCES

(1) Marchlewski, L., and Mayer, J., *Bull. intern. acad. polon. sci.* (1929), p. 170.

(2) Regnier, J., Delange, R., and David, R., *J. pharm. chim.* (Paris), 23 (1936), 494.

Regnier, J., Brit. Pat. 477,882, 477,822; French Pat. 789,156.

Regnier, J., and David, R., *J. pharm. chim.*, 22 (1935), 16.

Regnier, J., and Quevauviller, A., *Compt. rend. soc. biol.*, 122 (1936), 251.

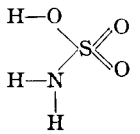
Regnier, J., Delange, R., and David, R., *Ibid.*, 202 (1936), 591.

Quinine Sulfamate*

By Kenneth H. Stahl† and R. A. Kuever‡

Sulfamic acid is gaining prominence in the fields of technical, industrial, medical and pharmaceutical chemistry (1). Its salts possess some advantages over the corresponding salts of the mineral acids.

The structure and properties of sulfamic acid are given by Butler, Smith and Audrieth (2) and Cupery (3). Empirically, it is HNH_2SO_3, and is made commercially by the reaction of urea and fuming sulfuric acid. Its graphic formula is:



Dry sulfamic acid is a stable, nonhygroscopic, crystalline product. It is moderately soluble in water and formamide, slightly soluble in ethanol, acetone and ether. It is insoluble in hydrocarbons, chlorinated hydrocarbons, carbon disulfide and sulfur dioxide.

The solubility of sulfamic acid in water is decreased by the presence of sulfuric acid or sodium sulfate. It is practically insoluble in 70% to 100% sulfuric acid.

When dissolved in water, sulfamic acid is highly ionized. The solutions are strongly acidic, and show high conductivity.

It is practically stable in water solutions at ordinary temperature. At elevated temperatures it is slowly hydrolyzed to ammonium acid sulfate.

Salts of sulfamic acid are stable in neutral or alkaline solutions, which may be evaporated on the steam bath without hydrolysis of the amide group. All of the known salts of sulfamic acid, with the exception of a basic mercury salt, are soluble in water.

With the properties of sulfamic acid in mind, two quinine sulfamates were prepared. These are quinine sulfamate and quinine bisulfamate. A study was made of the physical properties, solubilities in various solvents, molecular formula and crystalline structure. Some interesting properties were revealed, particularly with regard to solubilities in water and alcohol.

EXPERIMENTAL

Quinine sulfamate was prepared from equimolecular quantities of quinine and sulfamic acid: 378 Gm. of quinine was dissolved in 500 cc. of alco-

* Presented to the Scientific Section of the A. PH. A., Detroit meeting, 1941.

† Abstract from a thesis presented to the Graduate College of the State University of Iowa in partial fulfillment of the requirements for the degree of Master of Science.

‡ Professor, College of Pharmacy, State University of Iowa, Iowa City, Iowa.

hol, and 97 Gm. of sulfamic acid was dissolved in 750 cc. of water. The solutions were mixed, and evaporated to dryness on the steam bath. The crude salt thus obtained was crystallized from hot alcohol. The yield was practically theoretical.

Quinine bisulfamate was prepared from one mole of quinine and two moles of sulfamic acid. In using the procedure given above, the difficulty was encountered that decomposition of the sulfamic acid group took place on the steam bath at 80° C. To overcome this, the solution was evaporated at 40° C. under reduced pressure. The salt was prepared in the following manner: 378 Gm. of quinine was dissolved in 500 cc. of alcohol, and 194 Gm. of sulfamic acid was dissolved in 1500 cc. of water. The solutions were mixed and evaporated to dryness at 40° C. under reduced pressure, thus preventing decomposition of the amide group. The crude salt was crystallized from hot alcohol. The yield was practically theoretical.

Physical Properties.—Quinine sulfamate is a white, crystalline, odorless product with an extremely bitter flavor. It melts at 171–173° C. with decomposition.

The physical properties of quinine bisulfamate are similar to those of the sulfamate. It is a white, crystalline, odorless product, with a bitter flavor. It melts at 173–175° C. with decomposition.

Solubility Tests.—The solubility of both quinine sulfamate and bisulfamate in water, various organic solvents and several fixed oils was determined, using the standard methods. The organic solvents used were ether, benzene, chloroform and alcohol. The fixed oils used were olive oil and cottonseed oil. The solubility in oleic acid was also determined.

One gram of quinine sulfamate was found to be soluble in 10.8 cc. of water, 17.4 cc. of alcohol and 70.8 cc. of chloroform at 25° C. It was insoluble in benzene and ether at 25° C. It was found to be insoluble in olive oil, cottonseed oil and oleic acid at 25° C. and also at 60° C. Obviously, one important difference between quinine sulfamate and quinine sulfate is the greater solubility of the former in water and alcohol.

The solubilities of quinine bisulfamate were determined in the same manner. One gram of quinine bisulfamate was found to be soluble in 4.1 cc. of water and in 13.6 cc. of alcohol at 25° C. It was insoluble in benzene, chloroform and ether at 25° C. It was found to be insoluble in olive oil, cottonseed oil and oleic acid at 25° and 60° C. Again, it was found that quinine bisulfamate is more soluble in water and alcohol than quinine bisulfate.

Determination of Formula.—In determining the formulas of the two salts, several quantitative determinations were made. A Kjeldahl determination (3) for nitrogen was made on both salts. An official quinine content assay likewise was made. This assay consists of dissolving a 0.5-Gm. sample in water, and, after making alkaline with ammonia T. S., extracting the quinine with chloroform. The chloroformic extractions are evaporated on the steam bath, the residue is dissolved in ether and evaporated to dryness. The residue, consisting of anhydrous quinine, is dried to constant weight at 100° C., and determined gravimetrically.

Theoretically, the formula of quinine sulfamate is $C_{20}H_{24}O_2N_2 \cdot HNH_2SO_3$. The percentage of nitrogen found in the prepared product checked closely with the theoretical amount. The product prepared contained 5.4% of nitrogen, and the theoretical amount is 5.6%.

The sample of quinine sulfamate prepared assayed 65.4% of quinine. This agrees with the theoretical amount, which is 65.7% of quinine.

Theoretically, quinine bisulfamate is $C_{20}H_{24}O_2N_2 \cdot 2HNH_2SO_3$. The prepared sample of quinine bisulfamate was found to contain 8.5% of nitrogen. This agrees with the theoretical value, which is 8.8% of nitrogen.

The quinine content of the bisulfamate also checked closely with the theoretical value. The prepared product contained 51.2% of quinine, as compared to a theoretical value of 51.4%.

Both quinine sulfamate and bisulfamate contained one molecule of water of crystallization. A sample was dried to constant weight over sulfuric acid, and the percentage of water was determined.

The determinations described above establish the formula for quinine sulfamate as $C_{20}H_{24}O_2N_2 \cdot HNH_2SO_3 \cdot H_2O$, and quinine bisulfamate as $C_{20}H_{24}O_2N_2 \cdot 2HNH_2SO_3 \cdot H_2O$.

Crystalline Structure.—The crystalline structure of both salts was studied. The samples were prepared by spontaneous crystallization from water and alcohol. The crystals were examined microscopically.

Crystals of both salts are long, needle-like clusters, which grow in sheath-like bunches. They are sufficiently characteristic for purposes of identification and differentiation.

The crystalline structures of both salts from water and alcohol are shown in Figs. 1, 2, 3 and 4.

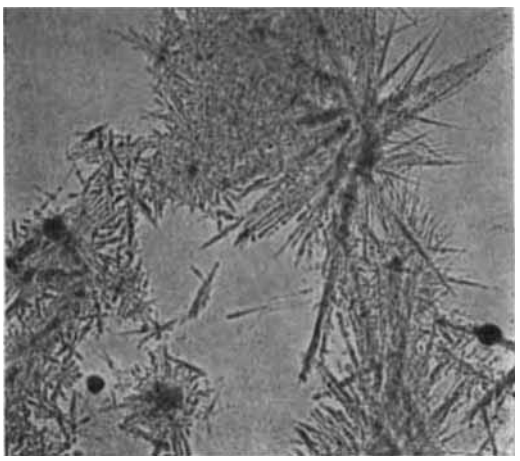


Fig. 1.—Quinine Sulfamate Crystals from Water. × 200.

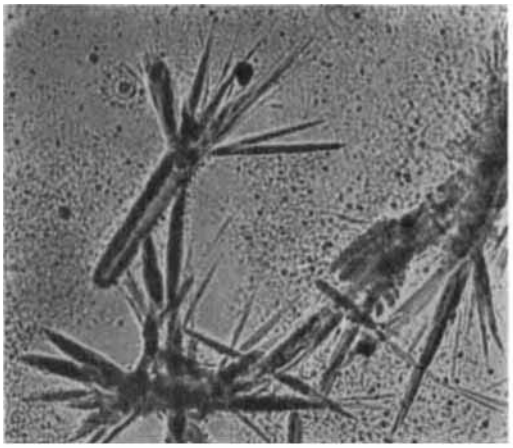


Fig. 2.—Quinine Sulfamate Crystals from Alcohol. × 200.

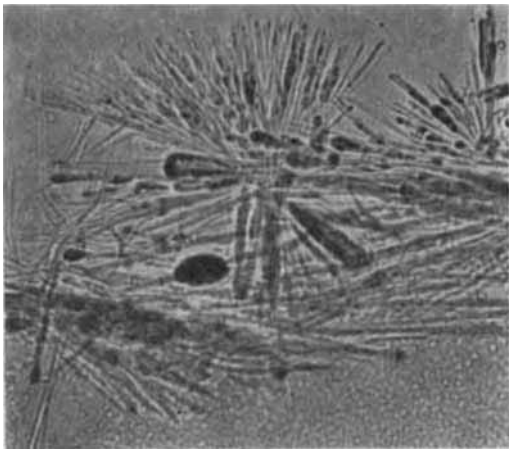


Fig. 3.—Quinine Bisulfamate Crystals from Water. × 200.

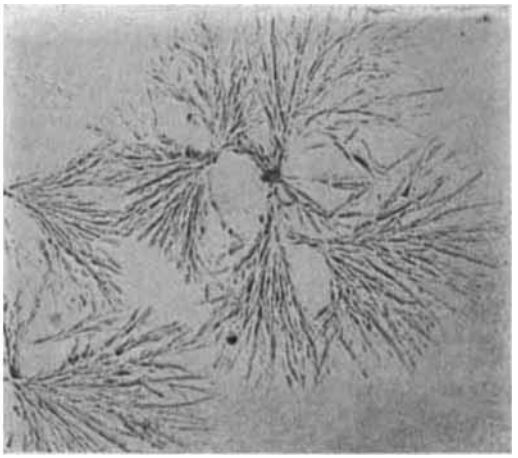


Fig. 4.—Quinine Bisulfamate Crystals from Alcohol. × 200.

SUMMARY

Quinine sulfamate and quinine bisulfamate have been prepared, identified and purified.

The preparation of quinine sulfamate is relatively simple. The preparation of quinine bisulfamate is somewhat more difficult. Its solution must be carefully evaporated under reduced pressure to prevent decomposition.

Both salts are white, crystalline, odorless products, with an intensely bitter flavor.

Both salts are more soluble in water and alcohol than the corresponding quinine salts of sulfuric acid.

The formula of quinine sulfamate has been established as $C_{20}H_{24}O_2N_2 \cdot HNH_2SO_3 \cdot H_2O$; of quinine bisulfamate as $C_{20}H_{24}O_2N_2 \cdot 2HNH_2SO_3 \cdot H_2O$.

The scope of this investigation did not include a study of the therapeutic properties of these two salts. Before they are employed as medicine, a complete pharmacologic investigation obviously is necessary.

REFERENCES

(1) Gordon, W. E., and Cupery, M. E., *Ind. Eng. Chem.*, 31 (1939), 1237–1238.

(2) Butler, M. J., Smith, G. F., and Audrieth, L. F., *Ind. Eng. Chem., Anal. Ed.*, 10 (1938), 690–692.

(3) Cupery, M. E., *Ind. Eng. Chem.*, 30 (1938), 627–630.

(4) "United States Pharmacopœia," Eleventh revision, 1936, pp. 317, 458.