Böeseken, Vermaas and Küchlin[3] have also determined the equilibrium constant for this complex formation from data on the potentiometric titration of boric acid in the presence of mannitol. They do not specify the temperature at which the measurements were made but report a value of 1.7×10^{-4} for K. Neither this result nor the result obtained by us are in agreement with that reported by Deutsch and Osoling.[1] The latter workers have defined K differently, but their K can be made equivalent to ours by multiplying it by the dissociation constant for boric acid. This gives for K, 0.33×10^{-4}, a value only one-third that obtained by us. Part but certainly not all of this difference can be attributed to the fact that our measurements were made in solutions of much higher ionic strength.

In making our calculations we have assumed that both B^- and BM^- are negligible compared to H^+ and BM_2. We have chosen concentrations of both boric acid and mannitol such that the hydrogen ion concentration is in every case at least ten times what it would be in the absence of the mannitol. Moreover, by using our determined value for the dissociation constant of boric acid and the Deutsch and Osoling value for the equilibrium constant, K_1, of the reaction

$$B^- + M \rightleftarrows BM^-$$

we can calculate the concentrations of B^- and BM^- and correct our equilibrium constant accordingly. We have not reported these revised values, since we strongly question the validity of the value of K_1 as determined by Deutsch and Osoling, and since these corrections would change our values by no more than 10% which is within our known experimental uncertainty.

(3) Böeseken, Vermaas and Küchlin, *Rec. Trav. Chim.*, **49**, 711 (1930).

RESEARCH LABORATORIES
THE SPRAGUE ELECTRIC COMPANY
NORTH ADAMS, MASSACHUSETTS RECEIVED JUNE 10, 1949

Boron Trifluoride Catalyzed Esterification of *p*-Aminosalicylic Acid

BY JOSEPH J. SCHAEFER AND LEONARD DOUB

The effectiveness of *p*-aminosalicylic acid (4-amino-2-hydroxybenzoic acid) in experimental tuberculosis chemotherapy[1,2] led us to prepare a number of its esters. These compounds have been prepared by reduction of the corresponding nitro esters,[3] but since *p*-aminosalicylic acid has become commercially available, it was desirable to investigate direct esterification. Conventional methods of esterification under various conditions led to very low yields,[4] the primary product being *m*-aminophenol.

Boron trifluoride as an esterification catalyst, following the work of Sowa and Nieuwland,[5] was tried and found to give excellent results. Approximately 70% yields were obtained with several alcohols. In general we used 4.5 moles of boron trifluoride for each mole of *p*-aminosalicyclic acid. In accord with the procedures of Sowa and Nieuwland, this provides one-half mole excess of boron trifluoride over that necessary for complex formation with the functional groups.

Experimental

Preparation of the Esters of 4-Amino-2-hydroxybenzoic Acid.—To a suspension of 153 g. (1.0 mole) of 4-amino-2-hydroxybenzoic acid in 1000 ml. of the anhydrous alcohol, 565 ml. (4.5 moles) of boron trifluoride–ethyl ether complex was added slowly, keeping below 40°. The resulting clear solution, after standing at room temperature for several days, was evaporated under reduced pressure to a thick slurry, and 500 ml. of water was introduced. Solution was effected by adding 10 *N* sodium hydroxide with cooling until alkaline to phenolphthalein. After charcoaling and filtering, solid carbon dioxide was added with agitation to precipitate the ester. This precipitate was removed by filtration and dissolved in dilute hydrochloric acid, charcoaled and filtered. The filtrate was neutralized with potassium bicarbonate. The ester precipitated, was filtered off and crystallized from ethyl alcohol.

ESTERS OF 4-AMINO-2-HYDROXYBENZOIC ACID

Ester	Reaction time, days	Yield, %	M. p., °C.	Empirical formula	Nitrogen, % Calcd.	Found
Methyl	10	74	121–122[4]	$C_8H_9NO_3$	7.73	7.88
Ethyl	10	71	114–115[5]	$C_9H_{11}NO_3$	8.38	8.27
Isopropyl	30	75	73–75[5]	$C_{10}H_{13}NO_3$	7.18	7.43 7.40

(4) Rosdahl, *Svensk Kem. Tid.*, **60**, 12 (1948), reports the preparation of the methyl ester with sulfuric acid in methyl alcohol. In our hands this procedure gave less than 10% yield.

(5) Sowa and Nieuwland, THIS JOURNAL, **58**, 271 (1936).

RESEARCH LABORATORIES
PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN RECEIVED JULY 1, 1949

(1) Lehmann, *Lancet*, **250**, 15 (1946).

(2) Youmans, *Quart. Bull., Northwestern Univ. Med. School*, **20**, 420 (1946).

(3) *Cf., e. g.*, Jensen, Rosdahl and Ingvorsen, *Acta Chir. Scand.*, **2**, 220 (1948).

The Melting Point of Potassium Hydroxide

BY RALPH P. SEWARD AND KENNETH E. MARTIN

The melting point of potassium hydroxide has been reported as 360° by Hevesy[1] and 380° by Scarpa.[2] A determination of the melting point of potassium hydroxide was suggested by the observation that a sample which had been heated several hours to remove water was found to remain solid above 400°. The observations which are recorded below indicate the melting point to be 410 ± 1°.

The "reagent" quality potassium hydroxide employed, from titration with standard acid, was found to be 86.5% potassium hydroxide and 1.0% potassium carbonate, which agreed with the maker's analysis. On heating to constant weight at a

(1) Hevesy, *Z. physik. Chem.*, **73**, 667 (1910).

(2) Scarpa, *Atti Acad. Lincei*, [5] **24**, 745 (1915); *C. A.*, **9**, 2828 (1915).

dull red heat, a weight loss of 12.5% was found. It was assumed that the only impurity present in significant amount after dehydration was the 1% of carbonate. To estimate the effect of the carbonate, freezing points were determined with known amounts of additional potassium carbonate.

About 50 g. of the hydroxide was melted in a nickel container brought gradually to 475–500°, and kept at this temperature ten to twelve hours to remove water. Further heating did not change the freezing point. The freezing points were obtained from cooling curves. Temperatures were measured with a chromel–alumel thermocouple which was calibrated at the freezing points of tin, lead and zinc, using Bureau of Standards samples. The same freezing point was found with and without a monel metal protecting tube around the couple. When a stream of dry nitrogen was passed over the hydroxide during dehydration and cooling, the freezing point did not differ from the freezing point of the hydroxide in contact with air. The observations are summarized in the accompanying table. The carbonate concentrations are not known with great precision because of the tendency of the molten hydroxide to creep up the walls of the container.

FREEZING POINTS OF KOH–K_2CO_3 MIXTURES

K_2CO_3, wt. %	1.0	4.9	7.0	12.2	16.2
F. p., °C.	408.0	400.0	394.5	384.2	373.5
Eutectic, °C.	358.7	365.0	365.0	366.9	366.5

By extrapolation, the freezing point of potassium hydroxide with no carbonate present was estimated to be 410°. A transition which Hevesy found at 248° and Scarpa at 360° was found at 249°. The heat of fusion calculated from the effect of carbonate on the freezing point was 1830 cal. per mole. Kelley[3] has calculated a value of 1980 cal. per mole from the data of Scarpa on the potassium hydroxide–potassium iodide system.

(3) Kelley, U. S. Bureau of Mines, Bulletin 393 (1936).

STATE COLLEGE, PENNSYLVANIA RECEIVED JUNE 3, 1949

Comparison of Some Properties of Thiolsulfonates and Thiolsulfinates

BY LAVERNE D. SMALL,[1] JOHN HAYS BAILEY AND C. J. CAVALLITO

The thiolsulfinates, R–SO–SR, have been shown to be active antibacterial and antifungal agents.[2] Although these oxides were previously unknown, the dioxides frequently have been described. These are now generally believed to have the thiolsulfonate structure, R–SO_2–SR. No record could be found of antibacterial tests with these compounds and it was of interest to compare the effect of the thiolsulfonate with that of the thiolsulfinate group in this respect.

The compounds used in this comparison were those where R was ethyl in the preceding structures. The thiolsulfonate was only 1.2% soluble in water compared with approximately 11% for the thiolsulfinate. This reduced interest in the higher alkyl thiolsulfonates. Both compounds react quickly with dilute alkalies.

Tests conducted by methods previously described[2] showed that the two thiol esters are of comparable antimicrobial activity, the thiolsulfonate being more effective against *S. aureus* and *K. pneumoniae*.

The antibiotic activity of thiolsulfinates has been attributed to the ability of the compounds to react with biologically essential –SH groups as exemplified by the reaction with cysteine to yield derivatives of type I, R–S–S–CH_2–$CH(NH_2)$–COOH.[3] With the thiolsulfinates one mole of compound yielded, nearly quantitatively, two moles of I. Under similar conditions the thiolsulfonate gave only one equivalent of I and an acid, presumably ethanesulfinic acid. This in harmony with the observations of Smiles and coworkers[4] who found that thiolsulfonates reacted with mercaptans to yield one mole of disulfide and one of the sulfinic acid. The ability of thiolsulfinates to react rapidly with cysteine (thiols) to yield two moles of I is further support of Smiles' evidence that "disulfoxides" have a thiolsulfonate structure. A disulfoxide presumably would yield two moles of sulfenic acid as an intermediate (plus one cystine) and reaction with more cysteine would give two moles of I. As it is, only one mole of I and one of the sulfinic acid are formed under the conditions.

$$R{-}SO_2{-}SR + HS{-}CH_2{-}CH(NH_2){-}COOH \longrightarrow I + RSO_2H$$

$$R{-}SO{-}SR + HS{-}CH_2{-}CH(NH_2){-}COOH \longrightarrow I + RSOH$$

$$RSOH + HS{-}CH_2{-}CH(NH_2){-}COOH \longrightarrow I + H_2O$$

The observation of Toennies and Lavine[5] that cystine "disulfoxide" reacts with cysteine to yield a mole of cystine and one of cysteine sulfinic acid favors the thiolsulfonate structure for this compound. Tests in our Laboratories show that cystine dioxide also is inhibitory to bacterial growth. Such compounds may have an *in vivo* biological growth-control function if oxidation of

TABLE I

ANTIMICROBIAL ACTION OF THE THIOLSULFINATE AND THIOLSULFONATE

Compound	Inhibitory concentration,[a] mg. per cc. *Clostridium perfringens*	*Klebsiella pneumoniae*	*Staphylococcus aureus*	*Escherichia coli*	*Mycobacterium tuberculosis* H37Rv	*Trichophyton mentagrophytes*
$C_2H_5SOSC_2H_5$[b]	0.05	0.05	0.05	0.015	0.005	0.005
$C_2H_5SO_2SC_2H_5$	.05	.015	.005	.01	.005	.005

[a] Concentration producing complete inhibition of growth in serial dilution tests. [b] For preparation see [2].

(1) Present address: University of Nebraska, Lincoln, Nebraska.

(2) Small, Bailey and Cavallito, THIS JOURNAL, **69**, 1710 (1947).

(3) Cavallito, Buck and Suter, *ibid.*, **66**, 1952 (1944).

(4) Smiles and Gibson, *J. Chem. Soc.*, **125**, 176 (1924); Miller and Smiles, *ibid.*, **127**, 224 (1925).

(5) Toennies and Lavine, *J. Biol. Chem.*, **113**, 593 (1936).