but aside from this the technique used was the same as has been reported previously.[2] The results obtained are recorded in Table I and Fig. 1. They indicate the usefulness of the absorption spectrum as a means of identification of coronene.

(2) Brode and Patterson, THIS JOURNAL, **63**, 3252 (1941).

DEPARTMENT OF CHEMISTRY
OHIO STATE UNIVERSITY
COLUMBUS, OHIO

RECEIVED APRIL 30, 1942

The Preparation of Acetylsalicylyl Disulfide and Salicylyl Disulfide

BY BYRON RIEGEL AND HAROLD WITTCOFF[1]

Benzoyl disulfide has been reported to be efficacious[2] in the treatment of pruritus. In order to combine the seemingly advantageous features of the aspirin and salicylic acid residues with the disulfide linkage, the *o*-hydroxy and *o*-acetoxybenzoyl disulfides were prepared.

The most direct method of synthesis is the oxidation of the sodium salt of the thio acid, which is prepared by the interaction of the acid chloride and anhydrous sodium hydrogen sulfide. A good method for the preparation of aspiryl chloride which gave a 91% yield of material that melted at 60° in contrast to the value of 49–50° given by Lindemann and Schultheis[3] involved merely the action of purified thionyl chloride on acetylsalicylic acid catalyzed by a few drops of dry pyridine. The addition of hydrogen sulfide to an anhydrous ethanolic solution of sodium ethoxide proved to be a convenient method for the preparation of an anhydrous solution of sodium bisulfide (NaSH). When the acid chloride was added to the ethanolic solution of sodium bisulfide, an unexpected loss of the acetyl group occurred simultaneously with the formation of sodium thiosalicylate even though the bisulfide solution was acid to phenolphthalein. The sodium salt was oxidized directly to the desired disulfide by the addition of iodine to the alcoholic solution, from which the crystalline product precipitated immediately. On crystallization from ethylene chloride the salicylyl disulfide melted at 142°. Acetylation of this product gave acetylsalicylyl disulfide which on crystallization from 95% ethanol melted at 101.2°. In some respects this method is similar to that given by Moness, Lott and Christiansen[4] for the preparation of benzoyl disulfide.

Toxicity and skin irritation tests on these two compounds were performed by Dr. Edwin J. Fellows, Department of Pharmacology, Temple University, School of Medicine. He found them to be non-irritant when ointments in 25% concentration, with either petrolatum or hydrophilic base, were applied to the shaved skin of rabbits. Likewise acacia or fixed oil suspensions of these compounds, when injected intramuscularly into rats in doses of 400–800 mg. per kg. of body weight were non-toxic. However, preliminary clinical tests as antipruritics have not proved encouraging.

Experimental[5]

Acetylsalicylyl Chloride.—In a flask equipped with a reflux condenser which was connected to a gas trap was placed 100 g. of acetylsalicylic acid (aspirin), 1 g. of dry pyridine and 78 g. (10% excess) of thionyl chloride, purified by distillation from cottonseed oil. Gentle heating on a steam-bath initiated the reaction. Heating was then discontinued until gas no longer was evolved, after which the reaction mixture was refluxed for one-half hour. On distillation at 5 mm., 100 g. (91%) of colorless liquid was obtained which distilled at 115°. The acetylsalicylyl chloride solidified on long standing. Crystallization from dry benzene gave thick prisms which turned milky at 52° and fused to a clear liquid at 60°. Later it was found that the undistilled reaction product was of sufficient purity for the subsequent reactions.

Salicylyl Disulfide.—An ethanolic sodium hydrosulfide solution[6] was prepared by saturating with hydrogen sulfide a solution of 125 g. of sodium in two liters of anhydrous ethanol. Hydrogen sulfide addition, even though facilitated by mechanical shaking, required several days. The solution assumed a brilliant yellow color and did not redden moistened phenolphthalein paper. This solution, after filtering, was used directly for the next reaction.

The best yields were obtained when one mole of the acid chloride reacted with two moles of the sodium hydrosulfide. Since the acetyl groups were removed it seemed that stoichiometrical proportions of sodium hydrosulfide, four moles, should be used; however, this gave much poorer results. To an ice cold solution containing a two molar equivalent of sodium hydrosulfide was added 110 g. of acetylsalicylyl chloride slowly with stirring. There was an evolution of hydrogen sulfide, and sodium chloride and presumably sodium acetate precipitated. The suspension was centrifuged and the precipitate was washed two times with small quantities of anhydrous ethanol. To the yellow

(1) Smith, Kline and French Research Fellow.

(2) (a) L. Bory and M. Mesanguy, *Bull. soc. franc. dermatol. syphilig.*, **46**, 344 (1939); (b) L. A. Brunsting, *Collected Papers of the Mayo Clinic and the Mayo Foundation*, **32**, 768 (1940); (c) S. Amberg and L. A. Brunsting, *Military Surgeon*, **88**, 617 (1941).

(3) (a) H. Lindemann and W. Schultheis, *Ann.*, **451**, 241 (1927); (b) R. Anschütz, *ibid.*, **367**, 172 (1909); see also the following who did not record a melting point: (c) J. McConnan and A. W. Titherley, *J. Chem. Soc.*, **89**, 1333 (1906); (d) R. Wolffenstein, German Patent 277,659; (e) I. M. Heilbron and D. W. Hill, *J. Chem. Soc.*, 1705 (1927).

(4) E. Moness, W. A. Lott and W. G. Christiansen, *J. Am. Pharm. Assoc.*, **25**, 397 (1936).

(5) All melting points are corrected. Microanalyses are by Dr. T. S. Ma, University of Chicago.

(6) A. Rube, *J. Chem. Soc.*, **99**, 558 (1911).

supernatant liquid and washings, cooled in an ice-bath, was added solid iodine, in small portions, allowing each portion to react before adding more, until the brown color persisted for at least ten minutes. This required about 122 g. of iodine. The crystalline disulfide precipitate was filtered, washed with small portions of 95% alcohol and then with small portions of water until most of the yellow color was removed. The mother liquor on evaporation gave additional crops of substantially pure material. White glistening platelets formed on crystallization from ethylene chloride; temperatures above 80° were avoided because it was found that decomposition with subsequent discoloration of the product resulted. A yield of 65 g. (59%) of salicylyl disulfide melting at 142° (Pyrex capillary) was obtained.

Although the diacetyl derivative was expected, analyses indicated the free hydroxyl compound. This was confirmed by the following facts: attempted saponification did not alter the compound; the precipitate, originally supposed to be sodium chloride, weighed more than calculated due presumably to sodium acetate; and acetylation gave a new product (see below) analyzing correctly for the diacetate.

Anal. Calcd. for $C_{14}H_{10}O_4S_2$: C, 54.81; H, 3.28; S, 20.93. Found: C, 54.93; H, 3.45; S, 20.19, 20.38.

Acetylsalicylyl Disulfide.—To 0.64 g. of salicylyl disulfide were added 3.5 ml. of acetic anhydride and two drops of concd. sulfuric acid. On stirring, the disulfide dissolved and the stoppered flask was allowed to stand one-half hour. Crystals of the acetylated material started to settle and a pasty mass resulted on cooling. While continuing the cooling, water was added with vigorous stirring. The reaction mixture was allowed to stand one-half hour, filtered and the product crystallized from hot 95% ethanol. A yield of 0.79 g. (97%) melting at 101.2° was obtained.

Anal. Calcd. for $C_{18}H_{14}O_6S_2$: C, 55.37; H, 3.61; S, 16.42. Found: C, 55.61; H, 3.70; S, 16.41, 16.61.

CHEMICAL LABORATORY
NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS RECEIVED JANUARY 24, 1942

Crystalline Natural α-Tocopherol Acetate

BY C. D. ROBESON

In the course of work on the purification of tocopherols from natural sources, natural α-tocopherol acetate has been prepared in crystalline form. The procedure is published because it may be of assistance in the purification of synthetic α-tocopherol acetate, recently adopted as the international standard for the biological assay of vitamin E.[1] The preparation of natural or synthetic α-tocopherol acetate in crystalline form has not been reported in the literature to the writer's knowledge.

In the preparation, an α-tocopherol concentrate from a natural source (52.5 g., 68% α-tocopherol by Emmerie–Engel assay) was esterified with acetic anhydride (26 g.) in pyridine (9.5 cc.) for two hours at 75°. The reaction mixture was added to water and ether extracted. The extract was washed with 5% hydrochloric acid and water to remove pyridine. The residue after the removal of solvent was distilled in a cyclic molecular still and the fractions distilling at 130–180° at 3 μ pressure were combined for crystallization (35.9 g., $E^{1\%}_{1\,cm.}$ (286 mμ) = 35.6).

The acetate was crystallized from a 1.25% solution (g. per 100 cc.) in methyl alcohol at −30°. After recrystallization from a 2.5% solution in methyl formate at −30°, α-tocopherol acetate was obtained in needle-like crystals m. p. 26.5–27.5°; $E^{1\%}_{1\,cm.}$ (286 mμ) = 41.2; yield, 13.3 g.

By saponification in an atmosphere of nitrogen, α-tocopherol was obtained $E^{1\%}_{1\,cm.}$ (292 mμ) = 73.8. Analyzed by the Emmerie–Engel procedure, standardized against pure natural α-tocopherol, the preparation assayed 99.4% tocopherol. A sample of natural α-tocopherol prepared by another procedure had $E^{1\%}_{1\,cm.}$ (292 mμ) = 73. Thus the crystalline α-tocopherol acetate appeared to be pure.

COMMUNICATION NO. 32 FROM THE
LABORATORIES OF DISTILLATION PRODUCTS, INC.
ROCHESTER, NEW YORK RECEIVED MARCH 24, 1942

Synthesis of 4,4′-Diamidinostilbene Hydrochloride

BY PETER P. T. SAH

4,4′-Diamidinostilbene has been prepared by the action of ammonia or ammonium salts on the bis-iminoether hydrohalides of 4,4′-dicyanostilbene.[1]

In this communication, an alternative route to the diamidine, a substance of recent pharmacological interest,[2] is described. *p*-Iodobenzaldehyde, from *p*-iodobenzonitrile[3] by Stephen's method, is converted through pyrolysis of the corresponding azine to 4,4′-diiodostilbene. The latter, which may alternately be obtained from 4,4′-diaminostilbene by the Sandmeyer reaction, is transformed through its dimagnesium derivative on reaction with ethyl orthocarbonate into the hexaethyl bis-ortho ester of stilbene-4,4′-dicarboxylic acid. On treatment with ammonia, the bis-ortho ester is transformed into the desired

(1) Hume, *Nature*, **148**, 472 (1941).

(1) British Patent 510,097; *Chem. Abstr.*, **34**, 4079 (1940).
(2) Yorke, *Trans. Roy. Soc. Trop. Med. and Hyg.*, **33**, 463 (1940).
(3) Sah and Wang, *Rec. trav. chim.*, **59**, 365 (1940).