

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

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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

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

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., $E_{1\text{cm.}}^{1\%}$ (286 m μ) = 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°; $E_{1\text{cm.}}^{1\%}$ (286 m μ) = 41.2; yield, 13.3 g.

By saponification in an atmosphere of nitrogen, α -tocopherol was obtained $E_{1\text{cm.}}^{1\%}$ (292 m μ) = 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 $E_{1\text{cm.}}^{1\%}$ (292 m μ) = 73. Thus the crystalline α -tocopherol acetate appeared to be pure.

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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*-iodobenzonitrile³ 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) 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).

4,4'-diamidinostilbene, which is isolated in crystalline form as the dihydrochloride.

***p*-Iodobenzaldehyde.**—The following method^{4a} is based on Williaus' modification^{4b} of the Stephen method.

Pure anhydrous *p*-iodobenzonitrile³ (15.5 g.) was treated with 30 g. of stannous chloride in 200 cc. of absolute ether. After saturation with dry hydrogen chloride, the stannic chloride aldimine hydrochloride complex was collected and subjected to steam distillation. After repeated purification by steam distillation and recrystallization from dilute ethanol, a very pure product (ca. 10 g.) was obtained; white needles, m. p. 77–78°.

Anal. Calcd. for C₇H₅OI: I, 54.74. Found: I, 54.64. Semicarbazone, white needles from 50% ethanol, m. p. 225°; Willgerodt and Rieke⁵ give 224.5°. Oxime, white needles from 50% ethanol, m. p. 111–112°; Patterson^{4a} gives 111°. In the preparation of the azine, the use of hydrazine hydrate (40%) was preferable to hydrazine sulfate and alkali, as used by Willgerodt and Rieke⁵; yellow needles from 50% ethanol, m. p. 230–232° (dec.).

4,4'-Diiodostilbene.—(a) 4,4'-Diiodobenzaldazine (6 g.) was sublimed repeatedly until the melting point of the sublimate reached 258°. The sublimate was then crystallized from absolute ethanol-toluene, from which 2 g. of very pale yellow leaflets, m. p. 259–260°, separated. Meyer and Hofmann⁶ give 257–259°.

(b) Twelve grams of pure 4,4'-diaminostilbene⁷ was diazotized in dilute sulfuric acid solution, and the diazonium salt was decomposed with 20 g. of potassium iodide. The crude product (ca. 16 g.) was first sublimed and then recrystallized from ethanol-toluene. Pale yellow leaflets (ca. 10 g.), m. p. 258–260°, mixed with the product from (a), m. p. 258–260°.

Anal. Calcd. for C₁₁H₁₀I₂: I, 58.96. Found: I, 59.13.

4,4'-Diamidinostilbene Dihydrochloride.—To the Grignard reagent from 6 g. of 4,4'-diiodostilbene in absolute ether and 0.7 g. of pure magnesium, 15 cc. of ethyl ortho-carbonate was added, and the mixture was heated under reflux for two hours. After treatment with ice, extraction, drying, and removal of solvent, 2.5 g. of a sirupy oil was obtained. Analysis indicated that this oil was the impure bis-orthoester.

Anal. Calcd. for C₂₈H₃₀O₆: C, 76.32; H, 9.15. Found: C, 75.91; H, 8.70.

Since attempts to purify the ester resulted in decomposition, the crude material was treated directly with 100 cc. of absolute ethanol which had previously been saturated with dry ammonia. The mixture was heated at 30° for one week in a tightly stoppered thick-walled bottle. Removal of the solvent *in vacuo* on the water-bath left 1.2 g. of a brown micro-crystalline mass, of no sharp melting point or distinctive form.

(4a) Jackson and White, *Am. Chem. J.*, **3**, 32 (1881); Patterson, *J. Chem. Soc.*, **69**, 1005 (1896); Willgerodt and Bogel, *Ber.*, **38**, 3451 (1905); Willgerodt and Uckle, *J. prakt. Chem.*, [2] **86**, 276 (1912).

(4b) *This Journal*, **61**, 2248 (1939).

(5) Willgerodt and Rieke, *Ber.*, **38**, 1479 (1905).

(6) Meyer and Hofmann, *Monatsh.*, **38**, 156 (1917).

(7) Elbs and Hoesmann, *J. prakt. Chem.*, [2] **39**, 502 (1889).

Anal. Calcd. for C₁₅H₁₆N₄: N, 21.20. Found: N, 20.98.

Attempts to purify a small sample of the crude amidine by sublimation resulted in decomposition, with the evolution of ammonia, and the sublimation of a small amount of 4,4'-dicyanostilbene, m. p. 276–278°, mixed with an authentic sample, no depression.

The remainder of the crude product was converted into the dihydrochloride by treatment with saturated ethanolic hydrogen chloride (100 cc.), boiling for one hour, decolorizing with charcoal, and concentrating *in vacuo*. The white micro-crystalline prisms thus obtained (800 mg.) did not melt below 300°.

Anal. Calcd. for C₁₆H₁₈N₄Cl₂: N, 16.62. Found: N 16.56.

DEPARTMENT OF PHARMACOLOGY
PEIPING UNION MEDICAL COLLEGE
DEPARTMENT OF CHEMISTRY
FU JEN UNIVERSITY
PEKING, CHINA

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NEW COMPOUNDS

N,N'-Di-acetylsulfanyl- and N,N'-Di-sulfanyl-*l*-cystine

N,N'-Di-acetylsulfanyl-*l*-cystine.—This compound was prepared from *l*-cystine by the method described by Kies, *et al.*,¹ for the preparation of di-*p*-toluenesulfonyl-cystine. The quantities of material used were: 14.4 g. of *l*-cystine dissolved in 125 cc. of *N* NaOH; 35 g. of *p*-acetylaminobenzenesulfonyl chloride; 100 cc. of ether, and an additional 125 cc. of 2 *N* NaOH. The reaction was completed in three hours. The acetylsulfanyl cystine came out in a gummy mass which solidified around the stirring rod upon cooling. The moist gummy solid was dissolved in 100 cc. of boiling 95% alcohol and decolorized with Merck activated charcoal. Upon evaporation of the alcohol under reduced pressure white crystals separated; yield, 21–25 g. (56–66% of theoretical, based on cystine). The material was purified by solution in ammonia and precipitation with hydrogen chloride. The gummy mass which separated was dissolved in a minimum quantity of boiling 95% alcohol and decolorized with charcoal. On addition of ether the compound was precipitated in white crystals and dried in a vacuum desiccator over sulfuric acid. The acetylsulfanylcystine gave a negative Sullivan test for cystine and a positive nitroprusside reaction after reduction with sodium cyanide. It gave a negative reaction with 1,2-naphthoquinone-4-sodium sulfonate.² The substance dried in an oven at 120° melted at 204–206° (uncor.) with foaming and decomposition. The desiccator dried sample was used for the analysis.

Anal. Calcd. for C₂₂H₂₆O₁₀S₄N₄: S, 20.20; N, 8.83. Found: S, 20.27; N, 8.93.

N,N'-Di-sulfanyl-*l*-cystine.—3.6 g. of the acetylsulfanyl-*l*-cystine was refluxed with 25 cc. of 10% hydro-

(1) Kies, Dyer, Wood and Du Vigneaud, *J. Biol. Chem.*, **128**, 207 (1939).

(2) Schmidt, *ibid.*, **122**, 757 (1937–38).