half of the halogen added appeared as pyridine hydroiodide.

2. Each of the substituted β-ketoalkylpyridinium iodides was cleaved by action of aqueous alkali into a characteristic hydroxybenzoic acid. The reaction provides a new and efficient method for preparation of hydroxybenzoic acids.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK AND CO., INC.]

Hydrogenation of Compounds Containing Divalent Sulfur

BY RALPH MOZINGO, STANTON A. HARRIS, DONALD E. WOLF, CHARLES E. HOFFHINE, JR., NELSON R. EASTON[1] AND KARL FOLKERS

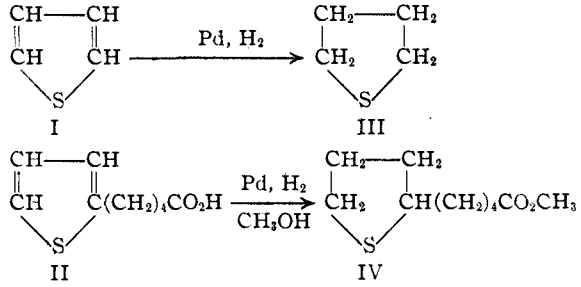
The occurrence of a sulfur atom in many natural products has led us to investigations of the hydrogenation of sulfur-containing compounds which would contain groups or structures representative of those which might be encountered in the synthesis of such natural products.

It became evident, after biotin had been shown to contain sulfur[2] and to be essentially a fully reduced compound,[3] that it might be useful to know catalytic methods for the hydrogenation of carbon to carbon double bonds and the like in sulfur-containing compounds, especially in thiophene derivatives.

The reduction of sulfur-containing compounds has been accomplished in the past largely by chemical reduction rather than catalytic hydrogenation due to the poisoning effect of reduced (divalent) sulfur on the catalysts. However, the catalytic hydrogenation of cystine to cysteine in the presence of hydrochloric acid has been reported.[4] Here the reduction was the hydrogenolysis over palladium of a disulfide to the mercaptan. The hydrogenation of compounds containing oxidized sulfur[5] over platinum or palladium and the reduction of sulfonic acids to mercaptans[6] have been reported. The use of sulfur-active catalysts in the Bergius process is well-known.[7] But practical laboratory methods for the hydrogenation of reducible groups in sulfides, generally applicable to large numbers of compounds, appear not to have been reported. A method for the hydrogenation of carbon to carbon double bonds, carbonyls, and nitro groups and the reduction products of nitro groups, as well as hydrogenolysis of ring halogen, in divalent sulfur compounds has now been found. The method has been applied in the synthesis of biotin in this Laboratory.[8]

The choice of a catalyst for the hydrogenation of sulfur-containing compounds at a few atmospheres pressure[9] was limited, of course, to those catalysts which would cause hydrogenation under these conditions in sulfur-free compounds. Of the common catalysts, the oxide and sulfide catalysts are generally useful only in high pressure reactions, so only the various metal catalysts would be expected to be useful with hydrogen at, or near, atmospheric pressure. It has been shown that nickel removes the sulfur atom from sulfides[10] and for this reason appears to be not generally useful for hydrogenation of these compounds.

When various sulfides were submitted to hydrogenation it was found that palladium on carbon or palladium on barium sulfate is, under some conditions, active in the presence of sulfur-containing compounds. For example, thiophene (I) and 2-thiophenevaleric acid (II) were converted into the corresponding tetrahydro compounds (III and IV) by hydrogen and palladium on carbon. The nitro groups of 2,5-dibromo-3,4-



dinitrothiophene (V) were reduced in acid solution to amino groups and at the same time the halogen atoms in this compound underwent hydrogenolysis to give 3,4-diaminothiophene (VI). Because this diamine, as well as its salts, was readily oxidized in the air, it, therefore, was converted into the diacetamido (VII), dibenzamido (VIII) or imidazole (IX) derivative for isolation. Another example of such hydrogenation involving hydrogenolysis of a bromine atom was the reduction

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(2) Kögl, *Naturwissenschaften*, **25**, 465 (1937).

(3) Hofmann, Melville and du Vigneaud, *J. Biol. Chem.*, **141**, 207 (1941).

(4) Bergmann and Michalis, *Ber.*, **63**, 987 (1930); Kavanagh, THIS JOURNAL, **64**, 2721 (1942).

(5) Roblin and Winnek, *ibid.*, **62**, 1999 (1940).

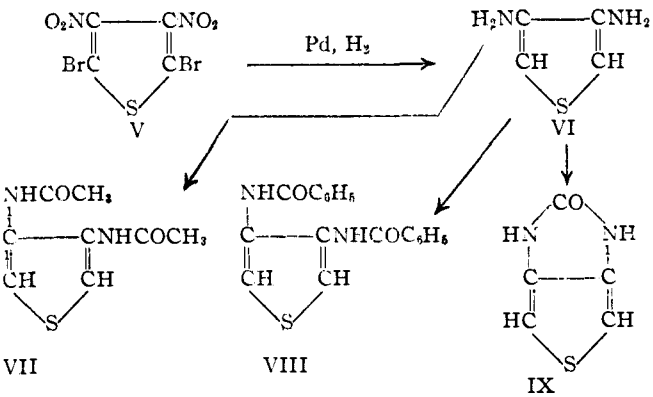
(6) Lazier and Signaigo, U. S. Patent, 2,221,804; *C. A.*, **35**, 1410 (1941).

(7) Ellis, "Hydrogenation of Organic Substances," D. Van Nostrand Co., Inc., New York, N. Y., 1930.

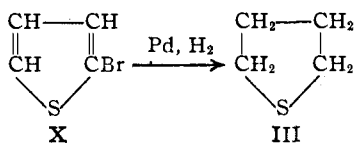
(8) Harris, Wolf, Mozingo, Arth, Anderson, Easton and Folkers, THIS JOURNAL, **67**, 2096 (1945).

(9) Because of the general availability of apparatus for low pressure (below 50 lb.) hydrogenation compared to that of stainless steel apparatus safe to use with sulfur compounds at high pressures, it appeared more desirable to operate in this low pressure region. Accordingly, the entire method has been worked out for this pressure range.

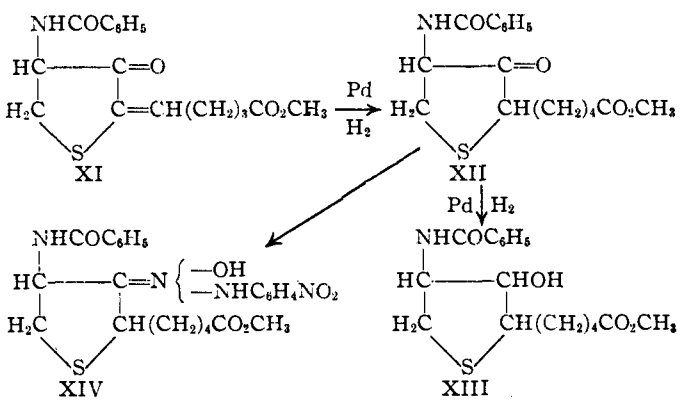
(10) Mozingo, Wolf, Harris and Folkers, *ibid.*, **65**, 1013 (1943).



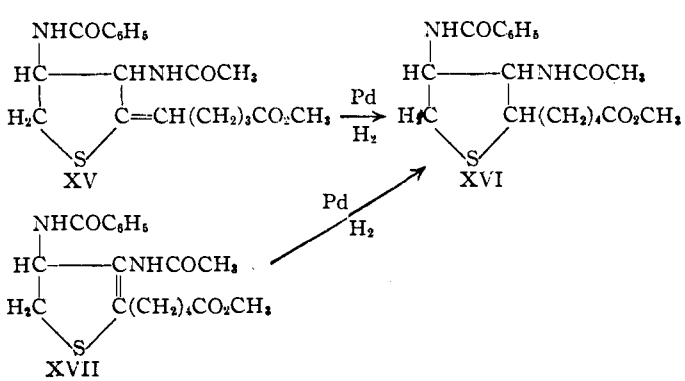
of 2-bromothiophene (X) to tetrahydrothiophene (III).



As certain of the unsaturated biotin intermediates[8] became available they were submitted



to hydrogenation. The methyl ester of 4-benzamido-3-keto-$\Delta^{2,6}$-tetrahydro-2-thiophenevaleric acid (XI) was converted into the saturated



ketone, the methyl ester of 4-benzamido-3-keto-tetrahydro-2-thiophenevaleric acid (XII), and this compound underwent further hydrogenation to the methyl ester of 4-benzamido-3-hydroxytetrahydro-2-thiophenevaleric acid (XIII). The latter of these reduction products was isolated in three of its four racemic forms. The ketonic nature of the first reduction product (XII) was demonstrated by preparation of the oxime and the *p*-nitrophenylhydrazone (XIV).

In the examples given above this reduction was usually carried out in the presence of mineral acid. However, this is not necessary as shown by the reduction of *dl*-allodehydro ester[3] (XV) in the absence of acid. The product of the reduction is a mixture of the *dl*-allodiamido ester (XVI) and the *dl-epi*-allodiamido ester (XVI).[8] The hydrogenation of the *dl*-isodehydro ester (XVII) by this method is described elsewhere.[8]

Experimental

Palladium Chloride on Darco Catalyst.—A solution of 86.6 g. of palladium chloride (containing 52 g. of palladium) was dissolved in 200 ml. of concentrated hydrochloric acid and 500 ml. of water. The solution was diluted to 1500 ml. with water and was poured into 1000 g. of nitric acid-washed Darco G-60. Enough water was added to make a mass just thin enough to be stirred. After the palladium chloride solution had been mixed thoroughly with the carbon, the whole mixture was dried in an oven at 100° with occasional mixing until completely dry. The mass was powdered and stored in a closed bottle; it was reduced in the solvent before use.

Palladium–Barium Sulfate Catalyst.—A solution of palladium chloride was prepared by dissolving 79.2 g. of palladium chloride (containing 47.5 g. of palladium) in 200 ml. of concentrated hydrochloric acid and 500 ml. of water by heating. After the palladium was in solution, the barium sulfate was prepared. To a hot solution of 1262 g. of reagent barium hydroxide octahydrate in 12 liters of water in a large Pyrex battery jar, 1200 ml. of 6 *N* sulfuric acid was added all at once. Enough more 6 *N* sulfuric acid was added to make the suspension just acid to litmus. The palladium solution and 80 ml. of formalin were added to the suspension of barium sulfate. The solution was then made slightly alkaline to litmus with 30% sodium hydroxide solution, constant stirring being maintained. The suspension was stirred five minutes longer, and the catalyst was allowed to settle. The supernatant liquid was siphoned away from the precipitate, was replaced by water and the catalyst was resuspended; this process was repeated eight to ten times. After allowing the solid to settle, as much water was removed as possible and the solid was collected on a filter. The filter cake was washed with 1 liter of water and was dried at 80° in an oven. It was stored in a tightly closed bottle.

Hydrogenation of Thiophene.—Ten grams of the palladium chloride on Darco catalyst was reduced in 200 ml. of methyl alcohol with hydrogen at 2–4 atmospheres. To the reduced catalyst and methyl alcohol were added 1.4 ml. of concentrated sulfuric acid and 0.42 g. of thiophene. Absorption of two moles of hydrogen required twenty to thirty minutes of shaking under 2–4 atmospheres of hydrogen. The catalyst was removed by filtration and washed on the filter with 20 ml. of methyl alcohol. The mercuric chloride addition product was prepared by heating the methyl alcohol filtrate and 2.7 g. of mercuric chloride at 45° until solution was com-

plete after which it was diluted to 500 ml. with water. After cooling the solution to 0°, long needles of the mercuric chloride addition product of tetrahydrothiophene were deposited. The precipitate was collected on a filter and was washed with a small amount of water. The product was recrystallized from methyl alcohol and melted at 129–130°. The yield was 1.26 g. (71%). This compound is reported[11] to melt at 124.5–125.5°.

Hydrogenation of 2-Bromothiophene.—Twenty grams of the palladium chloride on Darco catalyst was reduced in 200 ml. of methyl alcohol with hydrogen at 2–4 atmospheres. To the reduced catalyst and methyl alcohol was added 1.63 g. (0.01 mole) of thiophene. Absorption of 3 equivalents of hydrogen required four to five hours shaking under 2–4 atmospheres of hydrogen. The catalyst was removed by filtration and washed on the filter with 20 ml. of methyl alcohol. To the methyl alcohol filtrate was added 4.0 g. (0.015 mole) of mercuric chloride. When solution was complete it was diluted with water to 500 ml. After cooling the solution to 0°, long white needles of the mercuric chloride addition product of tetrahydrothiophene were deposited. The precipitate was collected on a filter and washed with a small amount of water. The product was recrystallized from methanol and melted at 129–130°. The yield was 2.0 g. (56%).

Hydrogenation of 2-Thiophenevaleric Acid.—Ten grams of palladium chloride on Darco in 200 ml. of methyl alcohol was reduced by shaking with hydrogen at 20–40 lb. pressure. To the catalyst suspension were added 0.3 ml. of concentrated sulfuric acid and 2.0 g. of 2-thiophenevaleric acid.[12] Hydrogenation at 18–40 lb. hydrogen pressure required about six hours for the theoretical quantity of hydrogen to be absorbed. The catalyst was removed by filtration and was washed with 20 ml. of methyl alcohol. The mercuric chloride addition product was prepared by adding 5.5 g. of mercuric chloride, heating the mixture until solution was complete and diluting to 500 ml. with water. The solution was cooled and the crystals which formed were removed. After recrystallization from methyl alcohol, the product melted at 85–86°. The yield of the mercuric chloride addition product of the methyl ester of tetrahydro-2-thiophenevaleric acid was 3.0 g. (58%).

Anal. Calcd. for $C_{10}H_{18}O_2SCl_2Hg$: C, 25.35; H, 3.83; S, 6.84. Found: C, 25.57; H, 3.84; S, 6.49.

2,5-Dibromothiophene.—This compound was prepared by a modification of the original method.[13] To a solution of 297 g. of thiophene in an equal volume of benzene was added 950 g. of bromine as rapidly as possible without loss of bromine vapor. After the evolution of hydrogen bromide became slow, 700 ml. of ethyl alcohol and 250 g. of sodium hydroxide were added and the mixture was refluxed sixteen hours. The solution was diluted with water, and the organic layer was separated and distilled through a column. There were obtained 152 g. of 2-bromothiophene, b. p. 158–162°, and 425 g. of 2,5-dibromothiophene, b. p. 200–210°.

2,5-Dibromo-3,4-dinitrothiophene.[14]—A stirred mixture of 400 ml. of concentrated sulfuric acid, 600 ml. of 20% fuming sulfuric acid and 325 ml. of fuming nitric acid (density 1.5) was cooled, and 350 g. of 2,5-dibromothiophene was added drop by drop so that the temperature remained at 20–30°, cooling being maintained by means of an ice-bath. After the 2,5-dibromothiophene had been added, the reaction mixture was poured onto ice and the precipitate was removed by filtration. After recrystallization from methyl alcohol, 144 g. of 2,5-dibromo-3,4-dinitrothiophene, m. p. 134–135°, was obtained.

Hydrogenation of 2,5-Dibromo-3,4-dinitrothiophene.—Thirty grams of palladium chloride on Darco was reduced in 300 ml. of methyl alcohol and 300 ml. of water under 20 lb. of hydrogen pressure for ten minutes. To the catalyst suspension was added 7.5 ml. of concentrated sulfuric acid followed by 10 g. of 2,5-dibromo-3,4-dinitrothiophene. The hydrogenation was carried out by shaking with hydrogen at 20 lb. for one to one and one-half hours after which hydrogen absorption was quite slow. The catalyst was removed by filtration and washed with 200 ml. of 50% methyl alcohol. The combined 50% methyl alcohol solutions were concentrated under reduced pressure to 200–300 ml. to remove all of the methyl alcohol. The resulting 3,4-diaminothiophene in acid solution was converted into its acetyl or benzoyl derivative for identification.

3,4-Diacetamidothiophene.—The water solution of the diamine from 30 g. of 2,5-dibromo-3,4-dinitrothiophene was treated with 105 g. of sodium bicarbonate and 60 ml. of acetic anhydride. The 3,4-diacetamidothiophene which crystallized was removed and the filtrate was concentrated to obtain a second crop. The combined material was recrystallized from acetone to constant melting point. The yield of 3,4-diacetamidothiophene, m. p. 207–208°, was 10.4 g. (58%).

Anal. Calcd. for $C_8H_{10}O_2SN$: C, 48.47; H, 5.09; N, 14.13. Found: C, 48.68; H, 5.26; N, 14.13.

3,4-Dibenzamidothiophene.—The water solution of the diamine from the hydrogenation of 10 g. of 2,5-dibromo-3,4-dinitrothiophene was covered with a layer of ether and 15 ml. of benzoyl chloride was added. The solution was made slightly alkaline with 30% sodium hydroxide, more being added from time to time so that only a slight excess was present. When the benzoyl chloride had all disappeared, the solid was removed by filtration and was recrystallized to constant melting point from acetone. In this way, 5.8 g. (60%) of 3,4-dibenzamidothiophene, m. p. 268–269°, was obtained.

Anal. Calcd. for $C_{18}H_{14}O_2SN_2$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.38; H, 4.26; N, 8.54.

2,3-Dihydro-2-oxo-1-thieno-(3,4)-imidazole.—The water solution of the diamine from the reduction of 1.7 g. of 2,5-dibromo-3,4-dinitrothiophene was treated with sodium carbonate and phosgene. The solution was concentrated to dryness and the product was extracted with methyl alcohol. The methyl alcohol was removed and the product was sublimed at 125–150° at about 10^{-6} mm. The sublimate was recrystallized from methyl alcohol–ether. The 2,3-dihydro-2-oxo-1-thieno-(3,4)-imidazole, m. p. 200° (micro-block), was obtained in low yields.

Anal. Calcd. for $C_5H_4OSN_2$: C, 42.84; H, 2.28; N, 20.04; S, 22.87. Found: C, 43.08; H, 2.82; N, 20.04; S, 22.48.

Methyl Ester of 4-Benzamido-3-ketotetrahydro-2-thiophenevaleric Acids.—A solution of 1.66 g. of 4-benzamido-3-keto-$\Delta^{2,5}$-tetrahydro-2-thiophenevaleric acid methyl ester in 200 ml. of methyl alcohol in which 10 g. of 5% palladium chloride on Darco G-60 had been previously reduced was shaken with hydrogen at 40 lb. pressure until one equivalent had been absorbed (about four hours). The catalyst was removed by filtration and was extracted repeatedly with methyl alcohol. After evaporation of the solvent and recrystallization from methyl alcohol–water, 0.5 g. of the saturated ketone, m. p. 114–116°, was obtained.

Anal. Calcd. for $C_{17}H_{21}O_4NS$: C, 60.87; H, 6.31; N, 4.18; S, 9.56. Found: C, 60.61; H, 6.29; N, 4.19; S, 9.86.

Methyl Esters of 4-Benzamido-3-hydroxytetrahydro-2-thiophenevaleric Acids.—The reduction of the methyl ester of 4-benzamido-3-keto-$\Delta^{2,5}$-tetrahydro-2-thiophenevaleric acid frequently proceeded further than the saturated ketone. In this case a mixture of isomeric carbinols was formed. The mother liquor from the reduction of the unsaturated ketone was allowed to evaporate gradually. The crystals which were deposited were taken up in ethyl alcohol and the alcohol solution was concentrated and cooled. The crystals of the carbinol which separated were recrystallized from benzene–ether. This carbinol melted at 127–128°.

(11) Grischkewitsch-Trochimowski, *J. Russ. Phys.-Chem. Soc.*, **48**, 901 (1923) [*Chem. Zentr.*, **94**, I, 1502 (1923)].

(12) Melville, Moyer, Hofmann and du Vigneaud, *J. Biol. Chem.*, **146**, 487 (1942); Fieser and Kennelly, THIS JOURNAL, **57**, 1611 (1935).

(13) Meyer, *Ber.*, **16**, 1469 (1883).

(14) Kreis, *ibid.*, **17**, 2974 (1884).

Anal. Calcd. for $C_{17}H_{23}O_4NS$: C, 60.53; H, 6.87; N, 4.15; S, 9.50. Found: C, 60.73; H, 6.84; N, 4.40; S, 9.75.

One of the crops of the saturated ketone was recrystallized from ether and the mother liquor was allowed to stand several days after which two types of crystals were obtained. The cubic crystals were separated from the needles of the saturated ketone mechanically and were recrystallized from methyl alcohol. This carbinol melted at 118–119°.

Anal. Calcd. for $C_{17}H_{23}O_4NS$: C, 60.53; H, 6.87; N, 4.15; S, 9.50. Found: C, 60.34; H, 6.93; N, 4.46.

Another carbinol was obtained by dissolving the crude saturated ketone in ether and allowing crystallization to take place by slow evaporation of the ether. The ether solution was decanted, and the crystals were recrystallized from methyl alcohol. This carbinol melted at 136–138°.

Anal. Calcd. for $C_{17}H_{23}O_4NS$: C, 60.53; H, 6.87; N, 4.15; S, 9.50. Found: C, 60.77, 60.84; H, 6.78, 7.03; N, 4.16; S, 9.39.

Methyl Ester of 4-Benzamido-3-oximinotetrahydro-2-thiophenevaleric Acid.—A solution of 209 mg. of 4-benzamido-3-ketotetrahydro-2-thiophenevaleric acid methyl ester in 5 ml. of absolute ethyl alcohol was treated with a slight excess of hydroxylamine hydrochloride and sodium acetate and was heated on a steam-bath for thirty minutes. After diluting the solution with water and cooling, feathery crystals of the oxime, m. p. 160–161°, separated.

Anal. Calcd. for $C_{17}H_{22}N_2O_4S$: C, 58.26; H, 6.33; N, 8.00; S, 9.15. Found: C, 58.30; H, 6.33; N, 7.83; S, 9.38.

The filtrate from the reduction of the unsaturated ketone was treated directly with hydroxylamine hydrochloride and sodium acetate, and the solution was heated on a steam-bath for one-half hour. After diluting with water and cooling, crude crystals were obtained. After crystallization from ethyl acetate, the first crop was the oxime, m. p. 161–162°, described above. The mother liquor was evaporated to one-half its volume and was left in a refrigerator overnight. This process of concentrating and cooling was repeated three more times to give four fractions. The third fraction was washed with boiling ether and recrystallized from methanol–water to give a second oxime, m. p. 152–154°.

Anal. Calcd. for $C_{17}H_{22}N_2O_4S$: C, 58.26; H, 6.33; N, 8.00. Found: C, 58.36; H, 6.28; N, 7.90.

This second oxime has a different crystalline structure from the oxime melting at 161–162°, and the melting point of a mixture of the two was definitely lower. The compounds are isomeric. The final ethyl acetate mother liquor gave the carbinol melting at 136–138° described above.

4-Benzamido-3-oximinotetrahydro-2-thiophenevaleric Acid.—A solution of 3.5 g. of 4-benzamido-3-oximinotetrahydro-2-thiophenevaleric acid methyl ester, m. p. 161–162°, in methyl alcohol was treated with 10 ml. of 2 *N* sodium methoxide and immediately with 4 ml. of water. After boiling for fifteen minutes, the reaction mixture was acidified with dilute hydrochloric acid to congo red. A crystalline product formed. The crystals were removed, were washed twice with methyl alcohol and were dried. The yield was 2.5 g. of oxime melting at 201°. The methyl alcohol mother liquor gave an additional 0.37 g. of the same compound after standing overnight.

Anal. Calcd. for $C_{16}H_{20}O_4N_2S$: C, 57.12; H, 5.99; N, 8.33. Found: C, 57.45; H, 5.63; N, 8.62.

***p*-Nitrophenylhydrazone of the 4-Benzamido-3-ketotetrahydro-2-thiophenevaleric Acid.**—A solution of 126 mg. of 4-benzamido-3-ketotetrahydro-2-thiophenevaleric acid methyl ester, in methyl alcohol was refluxed with one equivalent of *p*-nitrophenylhydrazine and one drop of concentrated hydrochloric acid. After standing for two days, 84 mg. of the *p*-nitrophenylhydrazone, m. p. 143–145°, was obtained.

Anal. Calcd. for $C_{23}H_{26}N_4O_5S$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.99; H, 5.73; N, 12.11.

Reduction of *dl*-Allodehydro Ester.—Five grams of the *dl*-allodehydro ester was hydrogenated over 20 g. of palladium–barium sulfate in 300 ml. of methyl alcohol. After four hours the absorption of hydrogen was complete. The catalyst was removed by centrifugation followed by filtration through supercel. The alcohol was concentrated under reduced pressure and crops of crystals were collected from time to time. Those crops melting below 175° weighed 1.40 g. and were recrystallized twice from methyl alcohol, from methyl alcohol–water, from isopropyl alcohol and again from methyl alcohol. After drying, the *dl*-allodiamido ester melted at 174–175° (micro-block).

The catalyst and supercel were re-extracted with 100 ml. of boiling methyl alcohol. After cooling the methyl alcohol solution, 1.75 g. of *dl-epi*allodiamido ester, m. p. 186–188°, was collected. Concentration of the mother liquor gave 0.7 g. of material which was recrystallized from methyl alcohol to give 0.45 g. more of this compound, m. p. 182–184°.

Anal. Calcd. for $C_{19}H_{28}N_2O_4S$: C, 60.29; H, 6.92; N, 7.43. Found: C, 59.97; H, 7.37; N, 7.50.

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Summary

It has been found that the carbon to carbon double bonds in thiophenes, biotin intermediates and other sulfides are hydrogenated by hydrogen and a supported palladium catalyst either in the presence or absence of a mineral acid. Under these conditions, nitro groups and carbonyls may be reduced. Preferential hydrogenation of the double bond in α,β-unsaturated ketones may be accomplished. The hydrogenolysis of the halogen in α-bromothiophenes simultaneous with reduction of the double bonds has been found to occur also under these conditions.

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