in a sealed tube at 68.8° for a period of ten half-lives, the solution being 0.176 *M* in ester and 0.122 *M* in hydrochloric acid. The acetone was removed by distillation, and the product was extracted with ether. The solution was dried and the solvent distilled. Distillation of the residue yielded 0.63 cc. of material, b.p. 90–110° (28–32 mm.). The 3,5-dinitrobenzoate of the material melted after two recrystallizations from ethanol,[15] at 117–118°; since benzyl 3,5-dinitrobenzoate is reported[16] to melt at 113°, the product was analyzed to be certain that it was the thiolester.

Anal. Calcd. for $C_{14}H_{10}N_2O_5S$: C, 52.82; H, 3.17. Found: C, 53.04; H, 3.23.

Acid-catalyzed Hydrolysis of Trityl Thiolacetate.—The product which crystallized from the aliquot titrated at the completion of a run was filtered and washed with water. It melted at 156–159°. When mixed with triphenylcarbinol it melted at 158–160°.

Alkaline Hydrolysis of Trityl Thiolacetate.—A 62% aqueous acetone solution, 0.041 *M* in sodium hydroxide and 0.0056 *M* in trityl thiolacetate was prepared from 0.178 g. of the thiolacetate. The solution was kept in an ice–water mixture for ten hours, then acidified with hydrochloric acid. The acetone was removed under reduced pressure. The oil which separated was extracted with C.P. ether, and the solution dried, then the solvent removed. The residual oil yielded only a minute crystalline product upon standing in the refrigerator; it melted at 183°. A semi-solid product was obtained from the remainder of the oil by crystallization from ethanol and water. By fractional crystallization from C.P. benzene and pentane, and decolorization with Filtrol, three fractions were obtained, only one of which was pure. The low melting fraction, 77–78°, upon recrystallization melted at 95–108°, then formed a higher melting product. A product melting at 177–178°, after two recrystallizations from benzene and pentane, was lost when a micro-crystallization tube broke in the centrifuge. The third product from the filtrate of the 177–178° material after recrystallization melted at 155–159°, and mixed with triphenylcarbinol melted at 155–159.5°.

Trityl Mercaptan in Alkaline 62% Aqueous Acetone.—A 62% aqueous acetone solution, 0.041 *M* in sodium hydroxide and 0.0023 *M* in mercaptan, was prepared from 0.063 g. of trityl mercaptan.[17] The solution was kept at 0° for ten hours and treated in the same manner as the thiolacetate. The melting point of the few crystals which formed by refrigerating the oil was 175–185°. An oily solid was finally obtained from the oil by recrystallization from ethanol and water. Fractional crystallization from benzene and pentane and treatment with Filtrol of the benzene solution gave triphenylcarbinol, melting after two recrystallizations at 162°. The melting point when mixed with commercial triphenylcarbinol was 160°. Subsequent fractions gave only impure carbinol with melting points of 156–160° and 155–159°.

Trityl Mercaptan in Dilute Hydrochloric Acid Solution.—Slightly impure trityl mercaptan (0.25 g.), m.p. 100–107°, dissolved in 104 g. of 62% aqueous acetone, 0.012 *M* in hydrochloric acid was refluxed 25 hours (about 10 half-lives) on a steam-bath. After the acetone was removed by distillation, the yellow oil which separated was extracted with ether. The crystalline product was recovered in 68% yield and melted at 75–80°. Crystallization from chloroform and hexane gave a 50% yield (based on the original wt. of mercaptan taken) of trityl mercaptan, m.p. 103–109°.

(15) Wertheim, THIS JOURNAL, **51**, 366 (1929), reports benzyl 3,5-nitrobenzoate to melt at 119–120.

(16) Huntress and Mulliken, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 471.

(17) The mercaptan, m.p. 106–107°, was generously given to us by Dr. N. Kharasch of the University of Southern California.

ROCHESTER 3, NEW YORK RECEIVED JUNE 19, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FRESNO STATE COLLEGE]

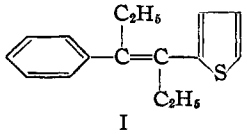
Some Thiophene Analogs of Diethylstilbestrol

BY W. R. BIGGERSTAFF AND OWEN L. STAFFORD

Two thiophene analogs of diethylstilbestrol, IIIa and IIIb, have been prepared. Physiological tests indicate that IIIa produces 50% estrus (rats) in 100γ doses (100% at 250γ). The benzene analog, 4-hydroxy-α,α′-diethylstilbene, has been reported[5b] to produce only trace activity at 100γ.

Other workers[1] have observed that the substitution of a 2-thienyl radical for a phenyl radical in certain physiologically active compounds may result in an enhanced activity.

During the course of a previous attempt to correlate structure and estrogenic activity[2] the effect of a 2-thienyl group in place of a phenyl group in α,α′-diethylstilbene was examined. The thiophene analog I[3] was tested and found to possess a low order of estrogenic activity.[4]



I

The conclusion was reached by these workers[2] that the substitution had resulted in a lowering of the estrogenic activity. However, in view of the relatively low estrogenic action of either α,α′-diethylstilbene[5a] or I this evidence appeared inconclusive and it seemed to us that additional data on related compounds might be useful.

Since the introduction of a 4-hydroxyl group into the α,α′-diethylstilbene nucleus greatly enhances its activity,[5b] it was thought that a similar introduction of the hydroxyl group into compound I should also produce an increased activity. Compounds IIIa and IIIb have now been prepared by following a previously described scheme.[6]

The acid chloride of α-(*p*-acetoxyphenyl)-butyric acid was condensed with thiophene to give, after hydrolysis of the acetate, the hydroxy ketone IIa

(1) (a) H. Y. Lew and C. R. Noller, THIS JOURNAL, **72**, 5715 (1950); (b) A. W. Weston, *ibid.*, **69**, 980 (1947); (c) F. F. Blicke and M. U. Tsao, *ibid.*, **66**, 1645 (1944); (d) Buu-Hoï, Nguyen-Hoán and D. Lavit, *J. Chem. Soc.*, 2130 (1950).

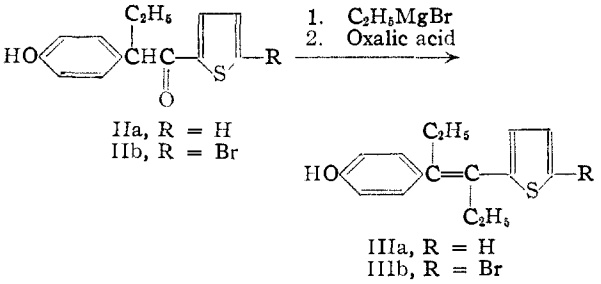
(2) L. Corre, Buu-Hoï, D. Guettier, A. Lacassagne, J. Lecoq, R. Royer and G. Rudali, *Bull. soc. chim. biol.*, **28**, 716 (1946).

(3) For the preparation of this compound (as an oil) see Buu-Hoï and Hiong-Ki-Wei, *Compt. rend.*, **220**, 175 (1945). Other thiophene analogs of stilbene have been reported (see ref. 1d).

(4) A 10-mg. dose produced estrus in mice.

(5) (a) M. Rubin and H. Wishinsky, THIS JOURNAL, **66**, 1948 (1944), have reported α,α′-diethylstilbene to be inactive at 1000 γ in rats; (b) 4-hydroxy-α,α′-diethylstilbene produces 100% estrus in rats at 1000 γ and only a trace at 100 γ according to E. C. Dodds, L. Golberg, W. Lawson and R. Robinson, *Proc. Roy. Soc.* (*London*), **B127**, 140 (1939).

(6) A. L. Wilds and W. R. Biggerstaff, THIS JOURNAL, **67**, 789 (1945).



in a 79% yield. A similar reaction with 2-bromothiophene led to the hydroxybromo ketone IIb (55%). Although it was possible to isolate the crystalline acetates, it was usually desirable to hydrolyze the coupling products directly to the free phenols. When the hydroxy ketone IIa was refluxed with an excess of ethylmagnesium bromide and the resulting complex was hydrolyzed, an oil was obtained which consisted of a mixture of the expected carbinol and its dehydration product; the dehydration was completed using 6% aqueous oxalic acid[7] and yielded an oily mixture of isomers of compound IIIa. The oil failed to crystallize from the usual solvents and an attempt to chromatograph the mixture on a talc-Filter Cel column followed by fractional elution also failed to produce a solid compound. Although the phenol was unstable to heat above 100°, the acetate was readily distilled at reduced pressure to give an analytically pure oil; however, attempts to separate the pure acetates by means of chromatographic adsorption on activated alumina followed by fractional elution and hydrolysis of the fractions also failed to produce crystalline IIIa. A solid 3,5-dinitrobenzoate of IIIa was finally obtained from the oily isomeric mixture.

The Grignard reaction with the bromo ketone IIb also resulted in an oily mixture of the isomers of IIIb which was less stable than compound IIIa. As before distillation of the acetate gave an analytically pure product.

Although it has generally been observed that acylation of thiophene occurs preferentially in the alpha position,[8] direct proof in the present case seemed desirable. Dichromate oxidation of IIIa acetate gave a low yield of 2-thiophenecarboxylic acid; however, a similar oxidation of the bromo derivative IIIb did not lead to an identifiable product and its structural assignment must depend upon the many known analogous reactions. Further work is under way which should establish this point more conclusively.

Physiological testing of the thiophene analogs for estrogenic action and pituitary inhibition has been conducted by Drs. R. K. Meyer and Elva G. Shipley of the department of zoölogy at the University of Wisconsin and is summarized in Table I.

These results show that the introduction of a hydroxyl group into compound I has resulted in a marked increase in estrogenic activity It is also interesting to note that IIIa appears to be more active than its benzene analog, 4-hydroxy-α,α'-diethylstilbene[8a] (*cf.* ref. 5b). The introduction of a bromine atom into each of the free 2-thiophene positions of IIIa acetate and IIa resulted in a decided lowering of their estrogenic activities as shown by the activities of IIIb acetate and IIb, respectively.

TABLE I

TESTING RESULTS

Compound	Dose γ	% Estrus (rats)	Pituitary inhibition (parabiotic rats)
IIIa	250	100	250 γ complete
	100	50	100 γ partial
IIIa acetate	250	100	75 γ complete
	100	73	
IIIb acetate	500	60	1000 γ partial
IIa	500	100	400 γ partial
	400	70	
	250	0	
IIb	1500	30	
	1000	0	1000 γ partial

Acknowledgment.—The authors wish to thank Drs. Meyer and Shipley for their kind assistance in testing the compounds and the Research Corporation for financial assistance which made the work possible.

Experimental[9]

1-(2-Thienyl)-2-(*p*-hydroxyphenyl)-1-butanone (IIa).—A solution of 10.02 g. of α-(*p*-acetoxyphenyl)-butyric acid[6,10] in 50 cc. of dry benzene was converted to the acid chloride by treatment with 10 cc. of thionyl chloride and two drops of pyridine at room temperature for four hours. After complete removal of the reagent,[6] the acid chloride was dissolved in 50 cc. of dry benzene and 3.6 cc. of thiophene. To the ice-cold solution was then added in one portion 6.6 cc. of anhydrous stannic chloride in 10 cc. of benzene. The mixture which separated into two layers upon swirling was allowed to attain room temperature over a period of one hour and was then diluted with ether and the complex hydrolyzed with cold 1:1 hydrochloric acid. The ether layer was washed with more acid and then with 5% ammonium hydroxide and dried over anhydrous sodium sulfate. The residual oily acetoxy ketone obtained after removal of the solvent was then hydrolyzed by refluxing with 35 cc. of 45% potassium hydroxide solution and 70 cc. of methanol for two hours. The alkaline solution was diluted with water and decolorized with Norit. Upon acidification 7.06 g. of the crystalline hydroxy ketone, m.p. 110–112°, was obtained; extraction of the filtrate gave an additional 1.75 g. of solid, m.p. 111–116°, bringing the total yield to 8.81 g. (79%). Recrystallization from benzene gave the pure ketone in the form of thick rectangular plates, m.p. 115–116.5°.

Anal.[11] Calcd. for $C_{14}H_{14}O_2S$: C, 68.3; H, 5.7. Found: C, 68.1; H, 5.7.

Other runs gave yields of 72–79% and although the crystalline acetate could be obtained directly, it was usually more convenient to isolate the hydroxy ketone as described above.

A sample of the **acetoxy ketone** was prepared (98% yield) from the purified hydroxy ketone by the use of acetyl chloride, acetic acid and pyridine. Recrystallization from benzene–petroleum ether gave the pure acetate as colorless blades, m.p. 87–88°.

(7) R. E. Miller and F. F. Nord, *J. Org. Chem.*, **15**, 89 (1950.)

(8) The preparation of 2-acetylthiophene in 83% yield, J. R. Johnson and G. E. May, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 8, and 2-acetyl-5-bromothiophene in quantitative yield, W. G. Emerson and T. M. Patrick, Jr., *J. Org. Chem.*, **13**, 722 (1948), may be cited as examples of alpha acylation; also see F. F. Blicke in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 217, 232.

(8a) Only a qualitative comparison should be made, however, since these two compounds were tested in different laboratories.

(9) All melting points are corrected.

(10) The authors wish to thank Dr. A. L. Wilds of the University of Wisconsin for a supply of the corresponding hydroxy acid which was used in this work.

(11) The analyses were conducted by the Analytical Division, Microchemical Specialties Co., Berkeley, California.

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.6; H, 5.6. Found: C, 66.3; H, 5.8.

The 2,4-dinitrophenylhydrazone of the above hydroxy ketone was prepared in the usual manner and upon recrystallization from ethanol was obtained as a red microcrystalline solid, m.p. 150–152°.

Anal. Calcd. for $C_{22}H_{18}N_4O_6S$: C, 56.3; H, 4.3. Found: C, 56.4; H, 4.4.

3-(2-Thienyl)-4-(*p*-hydroxyphenyl)-3-hexene (IIIa).—To 250 cc. of 0.18 molar ethylmagnesium bromide solution was added 2.00 g. of the hydroxy ketone IIa dissolved in 20 cc. of dry ether. The resulting mixture was refluxed for five hours during which time some of the solid that first formed dissolved. Hydrolysis of the reaction complex with saturated ammonium chloride solution followed by separation and removal of the ether (finally at 0.1 mm. and room temperature for two hours) gave an oil for which the analytical datum for carbon was intermediate between that for the carbinol and its dehydration product.

Anal. Calcd. for the carbinol $C_{16}H_{20}O_2S$: C, 69.5; H, 7.3. Found: C, 71.9; H, 7.4.

Dehydration of the above oil was completed by refluxing with 50 cc. of 6% aqueous oxalic acid for five hours.[7] The mixture was extracted with ether, and the extract washed with 5% sodium bicarbonate solution and dried over anhydrous sodium sulfate. Removal of the ether left 1.99 g. (95%) of an oily mixture of isomers which failed to crystallize from the usual solvents. The product was unstable above 100°; decomposition occurred in an attempt to distil the oil at 0.01 mm. A solution of 0.71 g. of the oily product in ligroin was passed through a column of 1:1 talc and Filter Cel which had been previously dried at 110° for two hours. Removal of the solvent (finally at 60° and 0.1 mm. for two hours) left a light yellow oil which was analyzed.

Anal. Calcd. for $C_{16}H_{18}OS$: C, 74.4; H, 7.0. Found: C, 74.0; H, 7.4.

An attempt was made to separate any unreacted ketone from the oily mixture IIIa using a Girard reagent but it was found in trial runs with the pure ketone IIa that neither the Girard reagent P nor T underwent reaction, even when a large excess of the reagent was used under prolonged refluxing. A negligible amount of ketone was probably present in the oil, however, since none of the previously prepared 2,4-dinitrophenylhydrazone of the ketone IIa could be prepared from the mixture.

The acetate of the unsaturated phenol IIIa was obtained using acetic acid, pyridine and acetyl chloride. The isomeric mixture distilled smoothly to give a straw-colored oil, b.p. 135–145° at 0.01 mm.

Anal. Calcd. for $C_{18}H_{20}O_2S$: C, 72.0; H, 6.7. Found: C, 71.8; H, 6.8.

Oxidation[12] of 1 g. of the acetate using sodium dichromate and sulfuric acid resulted in 55 mg. of a crude solid acid. Sublimation gave a sample of 2-thiophenecarboxylic acid, m.p. 125–127°, which did not depress the melting point of an authentic sample.

When 510 mg. of the phenol IIIa was treated with 461 mg. of 3,5-dinitrobenzoyl chloride in pyridine solution, 720 mg. of oily product was obtained which partially crystallized from alcohol to give 140 mg. of a solid, m.p. 80–90°. Repeated recrystallization from acetone–petroleum ether gave a pure **3,5-dinitrobenzoate** as clusters of pale yellow blades, m.p. 103–105°.

Anal. Calcd. for $C_{25}H_{20}N_2O_6S$: C, 61.0; H, 4.5. Found: C, 61.0; H, 4.4.

Attempts to prepare a solid urethan (α-naphthyl, phenyl and diphenyl) of IIIa met with failure. It was possible, however, to obtain the 2-thienyl chloromercuri substitution product as an impure solid; crystallization took place over a period of months.

1-(5-Bromo-2-thienyl)-2-(*p*-hydroxyphenyl)-1-butanone (IIb).—The acid chloride of 5.00 g. of α-(*p*-acetoxyphenyl)-butyric acid was prepared by the method described above and dissolved in 25 cc. of dry benzene, and 2.3 cc. of 2-bromothiophene was added to the solution.

The reaction was cooled in an ice-bath and 2.9 cc. of anhydrous stannic chloride in 5 cc. of dry benzene was added in one portion. The mixture was swirled in the ice-bath for one-half hour and then allowed to attain room temperature. The resulting dark purple complex was then hydrolyzed with 1:1 hydrochloric acid and the organic layer separated. After washing with 5% ammonium hydroxide solution and removal of the ether, the oily acetate was hydrolyzed by refluxing with 6 cc. of 45% potassium hydroxide and 25 cc. of methanol for 1.5 hours under an atmosphere of nitrogen. The solution was then cooled, diluted with water, acidified, and extracted with ether. Removal of the ether left a brown oil which was crystallized from alcohol to give in several crops 3.88 g. (55%) of the bromo ketone, m.p. 127–131°. Decolorization with Norit followed by several recrystallizations gave the pure ketone as colorless plates, m.p. 133–134°.

Anal. Calcd. for $C_{14}H_{13}BrO_2S$: C, 51.7; H, 4.0. Found: C, 51.9; H, 4.1.

The acetate of the bromo ketone was prepared in 91% yield using acetic acid, pyridine and acetyl chloride. Recrystallization from benzene–petroleum ether gave the pure acetoxy ketone in the form of long, colorless prisms, m.p. 95–96°.

Anal. Calcd. for $C_{16}H_{15}BrO_3S$: C, 52.3; H, 4.1. Found: C, 52.5; H, 4.2.

The 2,4-dinitrophenylhydrazone of the hydroxybromo ketone IIb was prepared in acetic acid solution and after several recrystallizations from 3:1 alcohol–benzene was obtained as orange microcrystals, m.p. 231–232°.

Anal. Calcd. for $C_{20}H_{17}BrN_4O_6S$: C, 47.5; H, 3.4. Found: C, 47.4; H, 3.5.

3-(5-Bromo-2-thienyl)-4-(*p*-hydroxyphenyl)-3-hexene (IIIb).—To a stirred solution of 60 cc. of 0.35 molar ethylmagnesium bromide was added 1.20 g. of the bromo ketone dissolved in 25 cc. of 1:1 benzene–ether. A yellow addition complex immediately precipitated and the mixture was refluxed for six hours. The suspension was cooled and the complex was hydrolyzed with a saturated ammonium chloride solution. Separation of the organic layer and removal of the solvent left 1.37 g. of an amber colored oil from which 130 mg. of the starting bromo ketone crystallized upon standing in benzene solution. Dehydration of the remaining oily product was completed as before by refluxing with 35 cc. of 6% aqueous oxalic acid for four hours. After extraction of the oil with ether, washing with 5% sodium bicarbonate solution, and removal of the ether, 1.00 g. of amber-colored oil was obtained. All attempts to crystallize the isomeric mixture failed. The oil was found to be unstable at temperatures above 80° although the solvent was successfully removed by warming the oil at 60° and 0.01 mm. for three hours; the viscous oil resulting from this treatment gave the correct analytical results for the desired bromo compound IIIb; however, considerable decomposition occurred upon long standing.

Anal. Calcd. for $C_{16}H_{17}BrOS$: C, 57.0; H, 5.1. Found: C, 56.8; H, 5.1.

The acetate of the above oily mixture was prepared and was purified by distillation to give a colorless oil, b.p. 120–130° at 0.01 mm.

Anal. Calcd. for $C_{18}H_{19}BrO_2S$: C, 57.0; H, 5.1. Found: C, 56.7; H, 4.9.

Attempts to prepare the 3,5-dinitrobenzoate and the phenylurethan failed to yield any solid products.

FRESNO 4, CALIFORNIA RECEIVED JULY 3, 1951

(12) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 198.