hydrochloric acid, distilled water, 95% ethanol, and ether. After drying at 50° *in vacuo* for forty-eight hours over phosphorus pentoxide, the ester weighed 53.0 g. (94% yield) and had the composition: % methoxyl calcd., 6.40; found, 6.85; % propionyl calcd., 38.4; found, 37.3; sapon. equiv. calcd., 99.0; found, 101.7.

In a further esterification, 47 g. of ester, 1000 ml. of pyridine, and 35 g. of propionic anhydride were shaken together for forty-eight hours at 20–24°. The pectin dipropionate was isolated and purified as before and had the composition: % methoxyl, 6.85; % propionyl, 38.6; sapon. equiv., 101.1; ash, 0.33%. A third esterification in which the ester was shaken for one week with pyridine and propionic anhydride gave a product with the propionyl content essentially unchanged, % propionyl 38.7; % methoxyl, 6.83.

Pectin Diacetate and Dibutyrate.—These esters were prepared by the reaction of pectin with the corresponding acid anhydride in pyridine under conditions essentially the same as for the dipropionate with the same molar proportions of reactants at 45–50° for three to five hours. The products were precipitated as fine flocs by pouring the reaction mixture into cold 3% aqueous hydrochloric acid. These esters were isolated by centrifuging and were purified by washing successively with 3% hydrochloric acid, distilled water, 95% ethanol, and ether. To ensure maximum acylations the esters were usually acylated a second time by shaking a solution of the ester in pyridine and acid anhydride for two days at room temperature as described in the preparation of pectin dipropionate.

Pectin Laurate, Myristate and Palmitate.—These esters were prepared from acid chlorides made by the procedure of Ralston[5] from Armour Neo-Fats. The preparation of a lauroyl ester of pectin is typical. Twenty grams of air-dry pectin, pretreated as described, reacted with 700 g. of pyridine and 200 g. of lauroyl chloride in a two-liter, three-neck flask. The acid chloride was added in small quantities throughout the course of the reaction. The reaction mixture was stirred vigorously for five hours at 55–60° and allowed to stand overnight. When the thick viscous mixture was poured into four liters of 3% hydrochloric acid, the ester and unreacted lauric acid coagulated at the surface as a brown sticky mass, which was stirred until coherent enough to be transferred into two liters of 95% ethanol. The alcohol was decanted and the partially granular product was washed repeatedly with 95% ethanol acidified with hydrochloric acid. It was purified by dispersion in 600 ml. of hot dioxane, followed by precipitation into two liters of absolute ethanol. A second purification in this manner yielded 34 g. of a pale-amber, waxy product containing no free lauric acid and having a lauroyl content of 49.4%, equivalent to 1.0 lauroyl group per repeating unit.

A second esterification in which 30 g. of this pectin laurate, 500 g. of pyridine, and 30 g. of lauroyl chloride were shaken together for two days at room temperature yielded 34 g. of ester having a lauroyl content of 53.1%, indicating a degree of esterification of 1.2 and a methoxyl content of 3.38%. The theoretical methoxyl content for this degree of esterification is 4.62%.

Pectin Benzoate.—Pectin was benzoylated by shaking a suspension of 15 g. of pectin in 600 g. of pyridine and 90 g. of benzoyl chloride for 36 hours at 20°. The mixture was poured into two liters of 95% ethanol and the hard resinous product was recovered by filtration. It was washed repeatedly with hot distilled water, hot 95% ethanol, acetone, and finally petroleum ether (30–60°). The ester was a hard amber-colored resinous material with a benzoyl content of 50.6%, indicating a degree of esterification of approximately 1.6 benzoyl groups per repeating unit. Methoxyl determinations gave inconsistent values, probably because of the insolubility of the ester in the Zeisel reagent.

The authors wish to thank R. M. McCready for uronic anhydride determinations.

Summary

1. A technique is described for the esterification of pectin.

2. Pectin diacetate, dipropionate and dibutyrate were prepared by esterification of citrus pectin with the acid anhydride in pyridine.

3. Lauroyl, myristoyl, palmitoyl, and benzoyl esters of citrus pectin have been prepared by esterification of pectin with the corresponding acid chloride in pyridine; the degree of esterification attained varied from 1.2 to 1.6 acid groups per anhydrogalacturonic acid unit.

ALBANY, CALIFORNIA RECEIVED FEBRUARY 12, 1945

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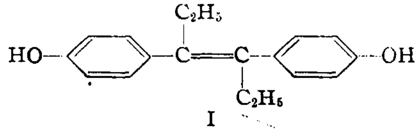
[5] Ralston, This Journal, **61**, 1019 (1939).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Diethylstilbestrol and its Monomethyl Ether

BY A. L. WILDS AND WARREN R. BIGGERSTAFF

The brilliant and fruitful investigations of Dodds and co-workers on synthetic compounds possessing the physiological action of the female sex hormone estrone were brought to a climax in 1938 by the discovery of diethylstilbestrol (I).[1] This compound was found to be of the same order of potency as estradiol, the most active of the naturally occurring hormones. Since 1938 much work has been done with the aim of improving the original synthesis of diethylstilbestrol reported by Dodds, Golberg, Lawson and Robinson and to develop other methods suitable for its commercial preparation.[2] Of the new approaches, that of Kharasch and Kleiman[3] is outstanding since it is reported to give diethylstilbestrol in 19 to 22% yield by a two-step process from readily available anethole.



I

In connection with the synthesis of certain related compounds, on which we hope to report at a later date, we were interested in further improvements in the original diethylstilbestrol synthesis of Dodds, *et al.*,[1] and particularly in modifications which would be suitable for preparing stilbenes

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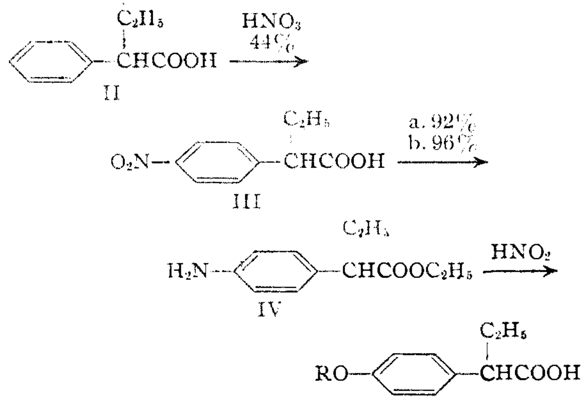
[1] Dodds, Golberg, Lawson and Robinson, *Nature*, **141**, 247 (1938); *Proc. Roy. Soc.* (London), **B127**, 140 (1939).

[2] This work has been reviewed recently by Jones, "Annual Reports on the Progress of Chemistry," 1943, p. 137.

[3] Kharasch and Kleiman, This Journal, **65**, 11 (1943).

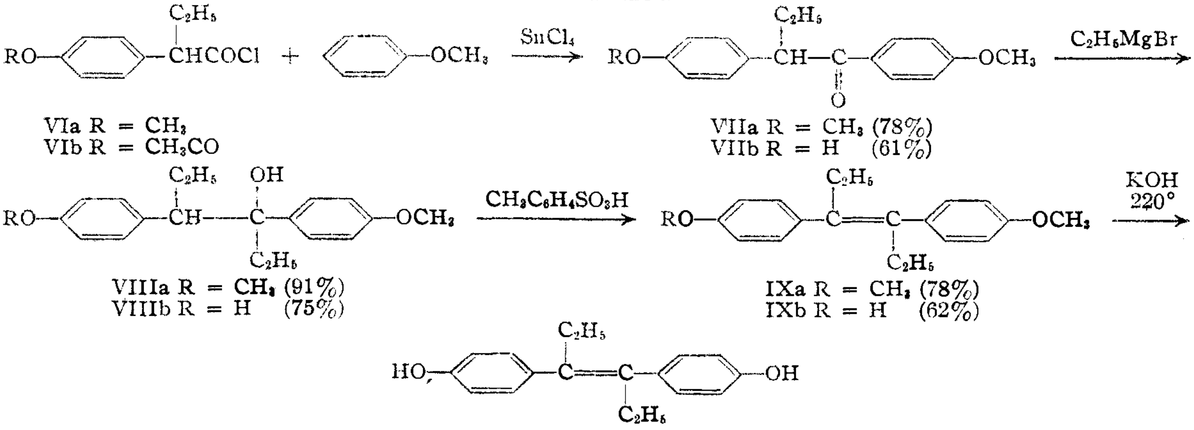
FLOW SHEET 1



V R = H (90% yield)
Va R = CH_3 (94% from V)
Vb R = CH_3CO (94% from V)

unsymmetrically substituted in the aromatic rings. The synthesis of Dodds, *et al.*, employed as the key intermediate α-ethyldesoxyanisoin (VIIa), which was prepared from anisaldehyde through anisoin and desoxyanisoin. The further steps in this synthesis are given by formulas VIIIa, IXa and I. We have made use of the well-known desoxybenzoin synthesis[4] to prepare α-ethyldesoxyanisoin, by condensing the acid chloride (VIa) of α-(*p*-methoxyphenyl)-butyric acid with anisole. The necessary acid Va, unknown at the time this work was undertaken,[5] was readily prepared from α-phenylbutyric acid (II), as indicated in Flow Sheet 1. The formation of derivatives of this acid as by-products in the preparation of phenobarbital, makes II a particularly suitable starting material. By condensation of VIa with anisole, we were able to prepare the crystalline para isomer of ethyldesoxyanisoin (VIIa).

FLOW SHEET 2



VIa R = CH_3
VIb R = CH_3CO
VIIa R = CH_3 (78%)
VIIb R = H (61%)
VIIIa R = CH_3 (91%)
VIIIb R = H (75%)
IXa R = CH_3 (78%)
IXb R = H (62%)

I (94% from IXa)

The subsequent steps in the synthesis were carried out as indicated in Flow Sheet 2 (Series a). In connection with the dehydration of the alcohol VIIIa and isomerization of the resulting mixture of isomers,[6] we have found *p*-toluenesulfonic acid to be quite suitable, particularly for small-scale runs. By the process given in Flow Sheet 2, the over-all yield of diethylstilbestrol from the methoxy acid Va was approximately 51%, or 17–26% from α-phenylbutyric acid.

This synthesis also was found to be adaptable to the preparation of the monomethyl ether of diethylstilbestrol (IXb). This derivative has been reported to be superior to diethylstilbestrol in some respects, particularly in that a considerably prolonged effect of the estrogen can be produced with a single large dose.[7] The preparation of the monomethyl ether has been reported in unspecified yields by partial methylation of diethylstilbestrol[8] or as a by-product from demethylation of its dimethyl ether.[9,9a] When the acid chloride of α-(*p*-acetoxyphenyl)-butyric acid (VIb) was condensed with anisole and the product hydrolyzed, the crystalline hydroxy ketone VIIb was obtained in 61% yield. In preliminary experiments the same ketone was obtained in 30 to 40% yields by partial demethylation of ethyldesoxyanisoin (VIIa) with hydrobromic acid. The lower susceptibility to cleavage of the methoxyl group para to the carbonyl group was unexpected.

The remaining steps in the synthesis were similar to those for diethylstilbestrol (Flow Sheet 2—Series b), with certain important modifications in procedure, given in the Experimental Section.

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[4] Allen and Barker, "Organic Syntheses," Coll. Vol. II, 156 (1943).

[5] Recently the paper of Mentzer and Urbain, *Bull. soc. chim.*, [5] **10**, 353 (1943), became available to us, reporting the preparation of Va from *p*-methoxybenzyl cyanide.

[6] (a) Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940); (b) Serini and Steinruck, U. S. Patent 2,311,093 (Feb. 16, 1943); (c) Rohrmann, U. S. Patent 2,346,048 (April 4, 1944); (d) Rohrmann, U. S. Patent 2,346,049 (April 4, 1944).

[7] (a) v. Pallos, *Arch. Gynäkol.*, **170**, 355, 385 (1940); (b) Geschickter and Byrnes, *J. Clin. Endocrinology*, **2**, 19 (1942).

[8] Reid and Wilson, THIS JOURNAL, **64**, 1625 (1942).

[9] Brownlee, Copp, Duffin and Tonkin, *Biochem. J.*, **37**, 572 (1943).

[9a] An improved procedure by Rubin, Kozlowski and Salmon, THIS JOURNAL, **67**, 192 (1945), has just appeared for this partial demethylation on a relatively large scale.

Experimental[10]

α-(*p*-Nitrophenyl)-butyric Acid (III).—A mechanically stirred and cooled solution of 400 g. of α-phenylbutyric acid[11] in 1460 cc. of concentrated sulfuric acid was treated over a period of two hours with 130 cc. of fuming nitric acid. The temperature of the solution was maintained at 0–10° by the addition of Dry-Ice. After another hour the mixture was poured onto ice and the crude solid filtered off, washed and dried; weight 495 g. (97%). This mixture of isomers was recrystallized three times from benzene–petroleum ether (Norit) to give a total of 222 g. (44%) of the para isomer, m. p. 118–121°. Further recrystallization from benzene gave the pure acid as pale yellow prisms, m. p. 121–122.5°. Chu and Marvel[12] reported the m. p. 118–120° for the acid and Fourneau and Sandulesco, 122–123°.[13]

Anal. Calcd. for $C_{10}H_{11}O_4N$: C, 57.4; H, 5.3. Found: C, 57.5; H, 5.2.

Oxidation of the acid with potassium dichromate gave *p*-nitrobenzoic acid; the acid (m. p. 236–238°) and its ethyl ester (m. p. 55–56°) showed no depression in m. p. when mixed with authentic specimens.

Ethyl α-(*p*-Nitrophenyl)-butyrate.—Esterification of 150 g. of the pure acid with alcohol and sulfuric acid gave 156 g. (92%) of the ester, b. p. 137–140° (0.4 mm.); 6 g. (4%) of unreacted acid was recovered (m. p. 118–121°). Redistillation gave the pure ester as a pale yellow liquid, b. p. 93–94° (0.01 mm.), $n^{27.5}_D$ 1.5162, $d^{27.5}_4$ 1.1341.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.7; H, 6.4. Found: C, 60.5, H, 6.4.

Ethyl α-(*p*-Aminophenyl)-butyrate (IV).—A solution of 80 g. of the nitro ester in 50 cc. of absolute alcohol containing 1 g. of Raney nickel catalyst was hydrogenated at 100–140° (200–350 atmospheres pressure). After removing the catalyst the ester was distilled giving 67–68 g. (96–97%), b. p. 127–129° (0.4 mm.). Redistillation gave the colorless ester b. p. 101–102° (0.05 mm.), n^{27}_D 1.5240, d^{27}_4 1.0450. Upon standing the amino ester became dark in color.

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 69.5; H, 8.3. Found: C, 69.6; H, 8.4.

A sample of the amino acid prepared by hydrolysis of the ester had the m. p. 141.5–143° (reported,[12,13] 142–143°).

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.0; H, 7.3. Found: C, 66.5; H, 7.1.

α-(*p*-Hydroxyphenyl)-butyric Acid (V).—A solution of 20 g. of ethyl α-(*p*-aminophenyl)-butyrate in 80 cc. of water containing 16 cc. of sulfuric acid was cooled to 5°. The suspension of the sulfate which separated from solution was diazotized by slowly adding 7.6 g. of sodium nitrite in 20 cc. of water with stirring. After ten minutes, the orange solution was added dropwise to a vigorously boiling mixture of 16 cc. of concentrated sulfuric acid and 320 cc. of water, contained in a 2-liter flask. The mixture was boiled under reflux for one and one-half hours longer and allowed to cool. The gummy solid was filtered, dried and recrystallized from benzene, giving 6 g. of acid melting at 122–126°. The oily residue from evaporation of the filtrate was treated with 5% sodium bicarbonate solution, extracted with ether and acidified; 5 g. of solid acid (m. p. 126–129°) was obtained by filtration, and by extraction of the filtrate additional material of the same m. p. was obtained bringing the total yield to 15.5–15.7 g. (89–90%). One recrystallization from benzene gave material with the m. p. 127–130°, satisfactory for the subsequent steps. The analytical sample, purified by evaporative distillation at 0.5 mm. and recrystallization from benzene, was obtained as thin, colorless leaflets melting at 129.5–130.5°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.6; H, 6.7. Found: C, 66.3; H, 6.7.

The pure hydroxy acid also was prepared by nitrating ethyl α-phenylbutyrate, using a procedure similar to that given above for the acid; the mixture of isomers of the nitro ester (yield 89%, b. p. 133–147° at 0.3 mm.) was hydrogenated in 97% yield to the amino ester (b. p. 133–135° at 0.4 mm.), and the latter was converted to the para hydroxy acid in 57–64% yield, m. p. 124–129°. This corresponds to an over-all yield of 46–52% from α-phenylbutyric acid, compared with 33% for the other method. Recrystallization gave the pure acid melting at 129.5–130.5°.

Ethyl α-(*p*-Hydroxyphenyl)-butyrate.—Esterification of 26.3 g. of the hydroxy acid with absolute alcohol and sulfuric acid gave 25.4 g. (84% yield) of the ester as a colorless oil, b. p. 131–135° (0.3 mm.), which crystallized on standing, m. p. 69–70°; 0.95 g. (4%) of the acid was recovered, m. p. 125–129°. Recrystallization of the ester from benzene–petroleum ether did not change the m. p. of the colorless leaflets.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7. Found: C, 69.3; H, 7.9.

α-(*p*-Acetoxyphenyl)-butyric Acid (Vb).—A solution of 10 g. of α-(*p*-hydroxyphenyl)-butyric acid in 40 cc. of acetic acid and 10 cc. of pyridine was treated with 10 cc. of acetyl chloride. After standing at room temperature overnight the mixture was poured into water; 10.51 g. of the acetoxy acid (m. p. 88–91°) was obtained by filtration and another 1.10 g. (m. p. 87–90°) by extraction of the filtrate and recrystallization from benzene–petroleum ether. The total yield was 94% of material suitable for use. Four recrystallizations from benzene–petroleum ether gave the acetoxy acid as colorless prisms which melted at 90.5–92°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.9; H, 6.4. Found: C, 64.8; H, 6.3.

α-(*p*-Methoxyphenyl)-butyric Acid (Va).—To a stirred solution of 27 g. of α-(*p*-hydroxyphenyl)-butyric acid in 270 cc. of 8% potassium hydroxide at room temperature was added 42 cc. of dimethyl sulfate in portions. The solution was kept alkaline by the addition of 25 cc. of 45% potassium hydroxide and stirred for forty minutes after all of the dimethyl sulfate had been added. Finally the alkaline mixture was refluxed for thirty minutes. Acidification of the now clear solution and cooling gave 28.3 g. of the methoxy acid, m. p. 62–67°. An additional 0.6 g. (m. p. 50–59°) was obtained by extraction of the filtrate. One recrystallization from petroleum ether (b. p. 60–68°) gave a total of 27.5 g. (94%) of the acid melting at 65–67°. Further recrystallization from benzene gave colorless needles with the m. p. 66–67° (Mentzer and Urbain reported the m. p. 68°).[5]

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3. Found: C, 68.0; H, 7.3.

Preparation of Diethylstilbestrol and its Dimethyl Ether[14]

α-Ethyldesoxyanisoin (VIIa).—A solution of 5 g. of the methoxy acid in 12 cc. of dry benzene was converted to the acid chloride by treating with 3.5 cc. of thionyl chloride and two drops of pyridine at room temperature for two hours and finally at 50° for five minutes. The excess thionyl chloride was removed under reduced pressure, 5 cc. of benzene added and evaporated, and the process repeated to remove the last traces of thionyl chloride. The acid chloride was then dissolved in 25 cc. of dry, thiophene-free benzene and 13 cc. of anisole, cooled in ice and treated with a solution of 10 cc. of anhydrous stannic chloride in 10 cc. of benzene. The mixture soon separated

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[10] All m. ps. are corrected.

[11] We are indebted to Dr. V. H. Wallingford of the Mallinckrodt Chemical Works for a supply of diethyl ethylphenylmalonate, from which we prepared most of the acid used in this work.

[12] Chu and Marvel, THIS JOURNAL, **55**, 2841 (1933).

[13] Fourneau and Sandulesco, *Bull. soc. chim.*, [4] **41**, 450 (1927).

[14] The abstract of German Patent 708,202 (June 5, 1941), *C. A.*, **37**, 2745 (1943) issued to Andersag and Salzer, describes in very general terms the condensation of a para substituted α-phenyl-α-alkylacetic acid with substituted benzene derivatives and conversion of the product into a stilbene derivative. The details of the patent are not available to us. This phase of our work was carried out prior to the appearance of the abstract.

into two layers and was allowed to stand at room temperature for twelve hours. The cherry-red mixture was then hydrolyzed with ice and hydrochloric acid, extracted with ether and the latter washed with dilute acid, sodium hydroxide and water. The solvent was removed and the oily residue was crystallized by seeding a solution in petroleum ether containing a small amount of benzene. (Seed crystals were obtained by distilling the oil under reduced pressure, dissolving in petroleum ether containing just enough benzene to give a clear solution at 0° and cooling and scratching the solution in a Dry-Ice-alcohol bath.) A total of 5.72 g. (78%) of colorless crystals was obtained melting at 46–48° to a cloudy liquid, clear at 63°.

After four recrystallizations from benzene-petroleum ether the m. p. of the α-ethyldesoxyanisoin still was 47–51°, giving a cloudy melt which cleared between 60 and 63°. Purification by adsorption on alumina from a solution in 95% petroleum ether (30–60°)–5% benzene and partial elution in about twenty fractions with solvents ranging from 90% petroleum ether–10% benzene to pure benzene, gave no evidence of separation into two components and the m. p. of the colorless prisms was 48–51°, clear at 58–60°. Long drying at 35° and 0.1 mm. did not change the m. p., but when a sample was melted at 90°, kept under reduced pressure for one hour, allowed to solidify, powdered and remelted, the m. p. was 46–50°, to a *clear* liquid. It would appear that the peculiar m. p. behavior is a characteristic of the compound. As far as we are aware the ketone has been reported previously in the literature only as an oil.[15]

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.0; H, 7.1. Found: C, 75.8; H, 7.0.

In agreement with most of the previous workers we were unable to obtain a crystalline oxime or semicarbazone from the ketone.[16] However, the 2,4-dinitrophenylhydrazone was obtained when 0.2 g. of the ketone was heated for one hour in 5 cc. of alcohol with 0.138 g. of the reagent and 0.14 cc. of concentrated hydrochloric acid. Upon cooling a red gum separated which crystallized from ethyl acetate–alcohol as orange blades melting at 121.5–122.5°; yield 0.30 g. (92%).

Anal. Calcd. for $C_{24}H_{24}O_6N_4$: C, 62.1; H, 5.2. Found: C, 61.9; H, 5.2.

3,4-Di-*p*-anisyl-3-hexanol (VIIIa).—A solution of 10 g. of α-ethyldesoxyanisoin (unrecrystallized; m. p. 46–48°) in 30 cc. of thiophene-free benzene was added to the ice-cold ethylmagnesium bromide prepared from 2.5 g. of magnesium in 60 cc. of ether. After standing at room temperature for twelve hours the mixture was hydrolyzed with cold ammonium chloride solution, extracted with ether and the product crystallized from alcohol to give a total of 10.12 g. (91%) of the mixture of diastereoisomeric alcohols, m. p. 70–100°. By fractional recrystallization from alcohol the two pure forms were obtained as colorless plates, m. p. 114–117° (reported 117°[1,6a]), and leaflets, m. p. 83–85.5° (reported 85°).[6a]

α,α'-Diethyl-*p*,*p'*-dimethoxystilbene (IXa).—The dehydration of 3,4-dianisyl-3-hexanol has been effected by a number of workers using phosphorus tribromide,[1] potassium bisulfate,[1,9a] potassium pyrosulfate,[6a] hydrogen chloride,[16] iodine[6d] and boron trifluoride[6c] as dehydrating agents. In those cases which were described in detail or for which yields were given, only a portion of the product was obtained directly in the form of the desired *trans*-stilbene derivative, and it was necessary to heat or treat the other isomerides[6a] in the filtrate again with one of these reagents in order to obtain the maximum conversion to the *trans* isomer.[17] We have found *p*-toluenesulfonic acid to offer some advantages over most of these reagents for small-scale laboratory runs. The mixture of stereoisomeric carbinols (10.3 g., m. p. 68–102°) was heated with 1 g. of *p*-toluenesulfonic acid in an oil-bath at 120–125° for thirty minutes. The melt which separated into two layers was stirred frequently. After cooling, the red mixture was treated with ether and water, whereupon the color lightened, and the extract was washed with sodium hydroxide and water. The partly solid product from the ether layer was recrystallized from ethyl alcohol to give 2.33 g. (24%) of the colorless stilbene derivative IXa, m. p. 121–124°. The second crop (2.4 g., m. p. 55–60°) consisted of a mixture of isomers of the dehydration product. The melting point range was widened to 53–70° by two recrystallizations of the material from alcohol.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.0; H, 8.2. Found: C, 81.1, H, 8.0.

The oily filtrate and the crystalline second crop (m. p. 55–60°) were combined and treated again at 125° with 2 g. of *p*-toluenesulfonic acid for thirty minutes. This resulted in an additional 4.14 g. of the desired stilbene derivative, m. p. 121.5–124°. A third and fourth treatment of the oil with 1 g. of the sulfonic acid gave 0.59 g. and 0.36 g., respectively, each melting at 119–123°. Further treatment with the sulfonic acid, or with iodine or hydrochloric acid,[6a] gave only a little more solid (0.17 g., m. p. 118–122°). The total weight of crystalline material (7.59 g.) corresponded to a yield of 78%. Essentially the same yield was obtained when the pure high-melting or the pure low melting isomer of the carbinol VIIIa was used. Recrystallization from alcohol gave the product as colorless leaflets melting at 123–124° (reported 123–124°,[1] and 127°[6a]).

α,α'-Diethyl-*p*,*p'*-dihydroxystilbene (Diethylstilbestrol—I).—The dimethyl ether was demethylated by heating and shaking 1 g. with 4 g. of potassium hydroxide and 10 cc. of ethyl alcohol in a steel bomb for twenty-two hours at 220°, essentially as described by Dodds, *et al.*[1]; yield 0.85 g. (94%) of diethylstilbestrol, m. p. 160–166°. Recrystallization from benzene gave colorless needles which changed to an amorphous powder when dried in vacuum, m. p. 169–170° (reported 171°,[1,6a]).

Preparation of the Monomethyl Ether of Diethylstilbestrol

1-(*p*-Anisyl)-2-(*p*-hydroxyphenyl)-1-butanone (VIIb).—Ten grams of α-(*p*-acetoxyphenyl)-butyric acid was converted to the acid chloride with 10 cc. of thionyl chloride and two drops of pyridine in 50 cc. of benzene, and the last traces of thionyl chloride removed as described above for the preparation of ethyldesoxyanisoin. A solution of the acid chloride in 30 cc. of dry, thiophene-free benzene and 25 cc. of anisole was then treated with 20 cc. of anhydrous stannic chloride in 20 cc. of benzene and allowed to stand for twelve hours at room temperature. The red mixture (two layers) was decomposed with ice and hydrochloric acid, extracted with ether and washed thoroughly with dilute acid and water. The oily residue after removal of the solvent was hydrolyzed by heating under nitrogen

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[15] It has been obtained crystalline, however, by at least one pharmaceutical company (The Abbott Laboratories).

[16] Kuwada and Sasagawa, *J. Pharm. Soc. Japan*, **60**, 93, *Abstracts*, 27 (1940), reported obtaining an oxime melting at 111°. However, since they obtained their ketone by treating the pinacol from anisoin and ethylmagnesium bromide with 50% sulfuric acid, it seems probable that the crystalline oxime actually corresponded to one of the other possible rearrangement products; *cf.* Péteri, *J. Chem. Soc.*, 833 (1940).

[17] In recent patents Rohrmann has claimed that dehydration of the carbinol (VIIIa) with iodine (ref. 6d) or boron trifluoride (ref. 6c) gave a product which was substantially all the *trans* stilbene derivative; the yields were not specified. While we have not been able to investigate these methods thoroughly, preliminary experiments on a small scale have not been entirely in agreement with these claims. With the boron trifluoride-ether complex at room temperature for five days, as described in the patent, a considerable amount of higher-boiling material was obtained from the carbinol and only part of the lower-boiling stilbene fraction was the desired *trans* isomer. With iodine (0.3% by weight), heated with the carbinol without solvent on the steam-bath for twelve hours, we obtained a 45% yield of the *trans*-stilbene derivative IXa, m. p. 112–119°; a second treatment with iodine gave an additional 19%, m. p. 118–122°, a third, 12%, and the fourth 6%, m. p. 113–119°. The total yield by this method was 82% in this case. Because of the simplicity of carrying out the reaction and the ease of isolating the product, this iodine method appears very attractive for large-scale runs.

with 10 cc. of 45% aqueous potassium hydroxide and 20 cc. of alcohol for two hours. The mixture was poured into water, acidified, extracted with ether and the latter washed with dilute sodium bicarbonate solution and water. After the ether was removed the residual oil was treated with petroleum ether until faintly cloudy and allowed to stand overnight in the refrigerator; 3.45 g. of the ketone, m. p. 95–108°, was obtained. Another 2.45 g. (m. p. 95–107°) of material could be crystallized from the filtrate. Evaporative distillation of the remaining oil at 0.3 mm. (discarding the anisole fraction distilling up to 110° at 0.3 mm.) and recrystallization of the distillate from benzene–petroleum ether gave an additional 1.46 g. of ketone, m. p. 95–104°, bringing the total crude yield to 7.36 g. (61%). One recrystallization from benzene gave 6.2 g. (51%) of material melting at 106–112°, which was satisfactory for the next step. Further recrystallization from benzene gave colorless leaflets which melted at 111–116°. The m. p. behavior was similar to that for α-ethyldesoxyanisoin; when the temperature of the bath was raised very slowly the crystals formed a semisolid cloudy mass at 111–112° which collapsed at 115.5° and was clear at 116°. The m. p. range was not changed by drying under vacuum, but when the material was melted, allowed to resolidify and powdered, the m. p. was 114–116°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.5; H, 6.7. Found: C, 75.2; H, 6.7.

The **3,5-dinitrobenzoate**, prepared in pyridine solution and recrystallized from petroleum ether–ethyl acetate, had the m. p. 112–115°, which was not sharpened by further recrystallization.

Anal. Calcd. for $C_{24}H_{20}O_8N_2$: C, 62.1; H, 4.3. Found: C, 61.9; H, 4.4.

Partial demethylation of α-ethyldesoxyanisoin led to the same monomethyl ether. One gram of the dimethoxy ketone was refluxed for six hours with 9 cc. of 40% hydrobromic acid and 17 cc. of glacial acetic acid. Upon cooling and addition of water until cloudy 0.33 g. of solid was obtained (m. p. 100–108°) and from the filtrate another 0.32 g. (m. p. 83–95°). Recrystallization from petroleum ether–ethyl acetate gave a total of 0.29–0.38 g. (30–40%) of material melting at 108–114°. Three further recrystallizations raised the m. p. to 111.5–114°, undepressed when mixed with the compound prepared above.

Anal. Found: C, 75.7; H, 6.7.

The 3,5-dinitrobenzoate had the m. p. 111–114°, undepressed when mixed with the derivative previously described.

When the filtrate from the monomethyl ether was diluted further and extracted with ether, 0.34 g. of oily dihydroxy ketone was obtained, which upon treatment with benzoyl chloride and recrystallization from alcohol gave the dibenzoate with the m. p. 138–140° (reported[1] 138–140). Like Dodds, *et al.*,[1] we were unable to crystallize the dihydroxy ketone, even when it was prepared by hydrolysis of the pure dibenzoate.

3-*p*-Anisyl-4-(*p*-hydroxyphenyl)-3-hexanol (VIIIb).—To a cooled solution of ethylmagnesium bromide, prepared from 1.8 g. of magnesium in 100 cc. of ether, was added in portions a solution of 2.0 g. of the hydroxy ketone (m. p. 106–112°) in 20 cc. of thiophene-free benzene and 10 cc. of ether. A white insoluble salt formed immediately. The mixture was refluxed vigorously for eighteen hours, during which time most of the solid disappeared, and then was hydrolyzed with ammonium chloride solution. The product was a light yellow oil which crystallized readily from benzene–petroleum ether to give 1.11 g. of material melting at 120–125°. A second crop of 0.56 g. (m. p. 100–120°) brought the total yield of the stereoisomeric alcohols to 75%. Recrystallization of the first crop from benzene–petroleum ether gave one of the pure isomers as colorless prisms, m. p. 124–125°.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 76.0; H, 8.1. Found: C, 76.2; H, 8.3.

α,α'-Diethyl-*p*-hydroxy-*p*'-methoxystilbene (Diethylstilbestrol Monomethyl Ether IXb).—In the case of this compound the dehydration with *p*-toluenesulfonic acid was more satisfactory and gave much better yields under reduced pressure than in air or under nitrogen (25–30% total yields in the latter cases). A 25-cc. suction flask, containing 1.2 g. of the above stereoisomeric alcohols (m. p. 100–120°) and 0.12 g. of *p*-toluenesulfonic acid, was evacuated to 0.1 mm. and placed in an oil-bath at 110–115°. In about two minutes the solids had formed a red melt which bubbled vigorously as water was removed. When the bubbling had stopped (approximately five minutes), the mixture was cooled and extracted with ether and water. The extract was washed with dilute sodium bicarbonate solution and water and the product was crystallized from benzene-petroleum ether; 0.29 g. of colorless needles was obtained, m. p. 111–114°. Retreatment of the oil with 0.1 g. of the sulfonic acid at 115° and 0.1 mm. for five minutes gave another 0.21 g. (m. p. 112–114°). Two further treatments gave 0.11 g. and 0.09 g., m. p. 112–114°, bringing the total yield to 0.70 g. (62%). Further recrystallization of the solid from benzene–petroleum ether raised the m. p. to 113.5–114°. Recrystallization from alcohol or alcohol-water gave colorless leaflets melting over a wide range (98–114°) when dried at room temperature, although further drying at 80° (0.1 mm.) for one hour raised the m. p. to 113.5–114°. Reid and Wilson[8] reported the m. p. 112–114° (from aqueous alcohol) or 116–117.5° (from benzene–petroleum ether) for the monomethyl ether prepared by partial methylation of diethylstilbestrol. Others have reported the m. ps. 120–121°[7a] and 114°[18] but without giving the method of preparation.

Summary

A modification of the original Dodds synthesis of diethylstilbestrol is described. The key intermediate, α-ethyldesoxyanisoin, has been prepared from α-(*p*-methoxyphenyl)-butyric acid and anisole.

This modification is adaptable to the synthesis of unsymmetrically substituted stilbenes. Its application to the preparation of the monomethyl ether of diethylstilbestrol is described.

MADISON 6, WISCONSIN RECEIVED JANUARY 22, 1945

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[18] Wessely, Kerschbaum, Bauer and Schlimke, *Naturwissenschaften*, **29**, 15 (1941).