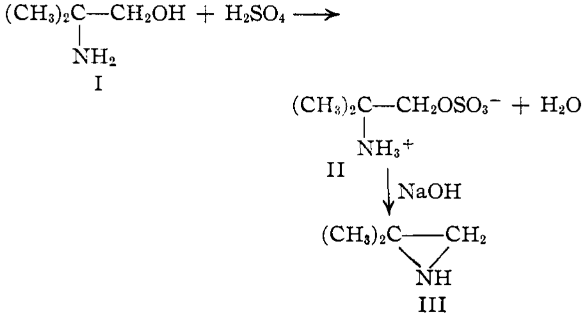
acid to give aminoethylsulfuric acid.[4] A similar procedure is used as the first step in the synthesis of 2,2-dimethylethyleneimine, but no published report of the actual identification of the reaction product has been made.

It has now been found that 2-amino-2-methyl-1-propanol (I) is esterified directly by sulfuric acid to give the expected 2-amino-2-methyl-1-propylsulfuric acid (II).



The mixture of the amine I, water and sulfuric acid was distilled slowly to remove the water according to the method of Cairns.[2a] The solid product obtained was identical with that formed during a more rapid distillation of the water similar to that described by Leighton, Perkins and Renquist[5] for the synthesis of β-aminoethylsulfuric acid. Both products yielded 2,2-dimethylethyleneimine (III) when treated with alkali.

The pure salt II was found to give no precipitate with barium chloride. This behavior parallels that of β-aminoethylsulfuric acid.[4] It was possible, however, to hydrolyze completely either β-aminoethylsulfuric acid or II in hot dilute hydrochloric acid containing barium chloride. This hydrolysis in the case of II yielded the hydrochloride of the amine I.

The possibility that the imine III might be an intermediate in the formation of the salt II was investigated. When 2,2-dimethylethyleneimine III reacted with sulfuric acid under conditions similar to those used in the preparation of II, a dark viscous product was obtained. None of the salt II could be isolated from the product, and no imine III was generated from it by alkali. It is clear from these results that the imine is not an intermediate in the preparation of II. The salt II, is formed directly from I, and III is produced by an intramolecular alkylation of II in the presence of alkali.

Experimental

2-Amino-2-methyl-1-propylsulfuric Acid (II).—A hundred grams (1.12 moles) of 2-amino-2-methyl-1-propanol (I) in 200 ml. of water was heated with 110 g. (1.06 moles) of sulfuric acid in 200 ml. of water until most of the water was distilled from the mixture. The temperature of the heating bath was then slowly raised to 175°, while the rest of the original water and that formed from the reaction was removed under the reduced pressure obtained with an aspirator. A modified method[5] was also carried out. Only about a quarter of the original amount of water was used. The solution of I was mixed with the slightly diluted sulfuric acid with cooling. The water was removed by distillation at reduced pressure over a free flame. In either case the light brown solid product was softened with 500 ml. of 95% alcohol, filtered and washed with absolute alcohol. Recrystallization from 50% alcohol yielded a white crystalline material which gave only a slight milkiness with aqueous barium chloride. The yield of purified product from the first procedure was 113 g. (63%); m. p. 253–255° (dec.).

Anal. Calcd. for $C_4H_{11}O_4NS$: C, 28.4; H, 6.56; N, 8.29. Found: C, 28.5; H, 6.48; N, 8.35.

Hydrolysis.—Two grams of II was dissolved in 25 ml. of water and 10 ml. of concentrated hydrochloric acid and 10 ml. of a saturated solution of barium chloride were added. The solution was heated overnight on a steam-bath. The barium sulfate was removed by filtration, and the filtrate was evaporated to dryness. The residue was recrystallized from absolute alcohol. The product had a m. p. 200–201° as compared with an authentic sample of 2-amino-2-methyl-1-propanol hydrochloride, m. p. 199–201°. There was no lowering of the m. p. on mixing the two. The recorded m. p. for the hydrochloride is 203–206°.[6]

Determination of Sulfur by Hydrolysis.—From 0.2 to 0.4 g. of the sulfuric ester was weighed and dissolved in 10% barium chloride solution so that there was 100% excess of barium chloride. Ten milliliters of 6 *N* hydrochloric acid was added and the solution was heated twenty hours on the steam-bath. The barium sulfate was determined gravimetrically. This analytical procedure was applied to the determination of sulfur in both II and β-aminoethylsulfuric acid.

Anal. Calcd. for $C_4H_{11}O_4NS$: S, 19.0. Found: S, 19.4, 19.8. Calcd. for $C_2H_7O_4NS$: S, 22.7. Found: S, 22.7.

Reaction of 2,2-Dimethylethyleneimine (III) with Sulfuric Acid.—A mixture of 57 g. (0.80 mole) of 2,2-dimethylethyleneimine[2] in 100 ml. of water and 79 g. (0.78 mole) of 96% sulfuric acid in 100 ml. of water was distilled with a water pump until the residue was a very viscous, black material. Treatment of some of this residue with alcohol gave no appreciable amount of crystalline product. Distillation of the residue from 40% sodium hydroxide (*ca.* 300% excess) gave some volatile material but little which distilled below 120°. 2,2-Dimethylethyleneimine boils at 70–72°.

Addendum.—It has been brought to our attention by one of the referees that J. V. Karabinos[7] has isolated 2-amino-2-methyl-1-propylsulfuric acid and β-aminoethylsulfuric acid from the reactions of the amino alcohols with sulfuric acid. Analysis of the esters for amino nitrogen by the Van Slyke method checked with the theoretical values.

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[4] Rollins and Calderwood, THIS JOURNAL, **60**, 2312, 2751 (1938).

[5] Leighton, Perkins and Renquist, *ibid.*, **69**, 1540 (1947).

[6] Jones, *J. Assoc. Official Agr. Chem.*, **27**, 467 (1944).

[7] Karabinos, "Dissertation," Ohio State University, 1946, p. 74b.

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF IOWA
IOWA CITY, IOWA

RECEIVED OCTOBER 20, 1947

The Friedel–Crafts Reaction on Highly Methoxylated Compounds

BY H. R. FRANK[1] AND D. S. TARBELL

The following observations give some information about the behavior of derivatives of anisole

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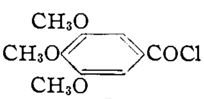
[1] Abbott Laboratories Fellow, 1946–1947.

and 1,2,3-trimethoxybenzene in the Friedel–Crafts reaction.

3,4,5-Trimethoxybenzoyl chloride (I) and anisole gave, with one and one-half moles of aluminum chloride, a mixture of the expected ketone (II) and a phenolic ketone. The position of the phenolic group in III was not established, but was assumed to be para to the carbonyl group, since the para methoxyl in 3,4,5-trimethoxybenzoic acid is cleaved in concentrated sulfuric acid, to give syringic acid (3,5-dimethoxy-4-hydroxybenzoic acid).[2] Aluminum chloride usually cleaves the methoxyl group ortho to the carbonyl in a substituted aromatic ketone or, if no ortho methoxyl is present, a para one. Ether linkages meta to a negative group are cleaved only at higher temperatures.[3]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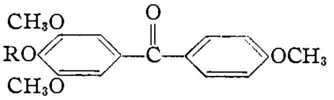
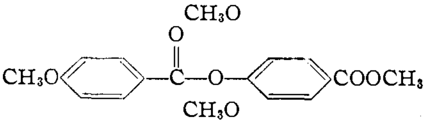
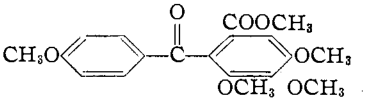

II, R = CH_3
III, R = H

When the acylation of methyl 3,4,5-trimethoxybenzoate with anisoyl chloride was attempted, no reaction was observed in the presence of one mole of aluminum chloride. The addition of a second mole caused reaction to occur; the product was a neutral compound, which, on hydrolysis, yielded anisic acid and syringic acid, and hence had structure IV. None of the desired keto ester V was obtained. Similar cleavage of ether linkages with ester formation has been observed before in attempted acylation of aromatic ether esters.[4] In the present case, the activating effect of the methoxyl groups in methyl trimethoxybenzoate is evidently not enough to compensate for the deactivating effect of the ester group, and make the ring susceptible to Friedel–Crafts acylation. However, Friedel–Crafts acylation of a substituted benzoic ester can occur if the substituents are more favorably placed than in the present case; thus, methyl 2,6-dimethoxy-4-methylbenzoate is reported to be acylated by acetyl chloride and aluminum chloride to yield methyl 2-hydroxy-3-acetyl-4-methyl-6-methoxybenzoate.[5]


IV


V

Experimental[6]

3,5,4′-Trimethoxy-4-hydroxybenzophenone (III) **and 3,4,5,4′-Tetramethoxybenzophenone** (II).—Freshly distilled 3,4,5-trimethoxybenzoyl chloride (I, 11.5 g., 0.05 mole) was dissolved in 10 cc. of anisole and 50 cc. of carbon disulfide. To this cooled solution was added 10 g. of aluminum chloride (0.075 mole, 50% excess) in small portions. Vigorous evolution of hydrogen chloride commenced, and a red complex formed in the solution. After refluxing on the steam-bath for ninety minutes, the reaction mixture was decomposed by ice-cold 1:3 hydrochloric acid, and the organic layer subjected to steam distillation to remove carbon disulfide and unreacted anisole. The residue was taken up in ether and extracted with dilute sodium hydroxide solution; a voluminous precipitate of the bright yellow sodium salt of the phenolic ketone, which appeared in the aqueous layer, was separated by filtration and the phenolic ketone regenerated with dilute acid. Crystallization from ethanol yielded 6.5 g. (45% yield) of colorless cubes of the phenolic ketone III, m. p. 163°. The product on methylation with dimethyl sulfate yielded the tetramethoxybenzophenone II.

Anal. (III). Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.60. Found: C, 66.59; H, 5.52.

Evaporation of the ether layer from the Friedel–Crafts reaction resulted in a sticky oil which partly crystallized when triturated with benzene or alcohol. Repeated recrystallization from methanol or ethanol yielded II, m. p. 75–77°. Since this material analyzed 1% low on carbon, it was refluxed with alcoholic alkali to remove any ester or phenolic compound. The recovered ketone melted at 76–77°, but the carbon percentage was unchanged; the phenylhydrazone was therefore prepared and analyzed. It melted at 170° after crystallization from alcohol.

Anal. Calcd. for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16. Found: C, 70.22; H, 6.35.

3,4,5,4′-Tetramethoxybenzhydrol.—Reduction of 3,4,-5,4′-tetramethoxybenzophenone in alcohol with zinc and concentrated ammonia, or zinc and sodium hydroxide, yielded after refluxing for two hours almost the theoretical quantity of the substituted benzhydrol, m. p. 106°, after crystallization from ethanol.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.13; H, 6.57.

The compound dissolves in concentrated sulfuric acid with a deep red color, which disappears on dilution with water.

2,6-Dimethoxy-4-carbomethoxyphenyl 4′-Methoxybenzoate (IV).—To a solution of 36.2 g. of methyl 3,4,5-trimethoxybenzoate in 75 cc. of benzene and 50 cc. of carbon disulfide was added 27 g. (0.16 mole) of anisoyl chloride in 100 cc. of carbon disulfide and 21.3 g. (0.16 mole) of aluminum chloride in small portions. The reagent dissolved, but no reaction was observed, even on refluxing. After cooling, another 21.3 g. of aluminum chloride was added to the reaction mixture. Evolution of hydrogen chloride took place smoothly. After the mixture had refluxed for one hour, the carbon disulfide was removed by distillation, and the residue decomposed with cold 1:1 hydrochloric acid. The neutral compound which separated was removed by filtration and washed with small portions of acetone. The benzene layer and acetone washings contained mainly starting material. The product after several crystallizations from ethanol melted at 171–173°.

Anal. Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 61.93; H, 4.93.

The structure was proved by hydrolysis with alcoholic alkali, which yielded two acids differing in their water solubility. The mixture of acids was dissolved in the minimum amount of boiling water, and cooled to 50°; anisic acid, m. p. 184°, separated. The solution, when cooled to room temperature yielded a small intermediate

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(2) Hahn and Wassmuth, *Ber.*, **67**, 696 (1934).

(3) Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publ. Corp., New York, N. Y., 1941, p. 727–728.

(4) Limpricht, *Ann.*, **290**, 164 (1896).

(5) Okazaki, *J. Pharm. Soc. Japan*, **59**, 547 (1939); *C. A.*, **34**, 1004 (1940).

(6) Analyses by Microtech Laboratories.

fraction, and cooling in ice gave fine needles of syringic acid, m. p. 209°.[7]

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(7) Syringic acid is reported to melt at 205° (uncor. ?).[2]

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ROCHESTER
ROCHESTER, NEW YORK RECEIVED NOVEMBER 21, 1947

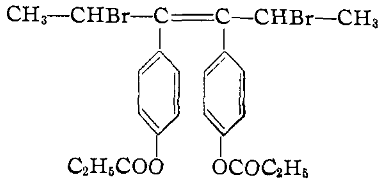
Introduction of Double Bonds into Diethyl Stilbestrol

BY M. J. FREIMAN

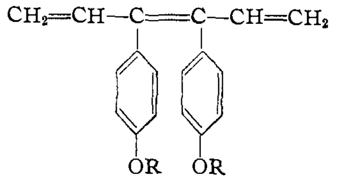
In the course of some work in this Laboratory on synthesizing substances with estrogenic activity, a 3,4 conjugated triene was prepared.

Diethylstilbestrol dipropionate was treated with 2 moles of N-bromosuccinimide to yield 3,4-bis-(*p*-propionoxyphenyl)-2,5-dibromohexene-3 (I). Two moles of hydrogen bromide were then eliminated by treatment with diethylaniline and the resulting 3,4-bis-(*p*-propionoxyphenyl)-hexatriene-1,3,5 (II) saponified to yield the free phenol (III).

The structural formulas of the new compounds are



I



II and III

II, R = C_2H_5CO—

III, R = H—

Absorption spectra of the conjugated triene dipropionate and the free phenol showed two peaks for each substance. The ester showed peaks at 273 and 280 mμ with a rather high molecular extinction coefficient of 22,860 at 280 mμ. The free phenol showed peaks at 223 and 257 mμ with a molecular extinction coefficient of 20,570 at 257 mμ.

Experimental

3,4-bis-(*p*-Propionoxyphenyl)-2,5-dibromo-hexene-3.—Thirty grams of diethylstilbestrol dipropionate dissolved in 300 ml. of carbon tetrachloride and 28.2 g. of N-bromo-succinimide were refluxed for thirty minutes in an atmosphere of nitrogen. The hot mixture was filtered and the crystals of succinimide washed with 15 ml. of carbon tetrachloride. The dried succinimide weighed 15.4 g. (theoretical recovery, 15.7 g.). The filtrate was washed with water to remove the last traces of succinimide, dried over sodium sulfate, filtered, concentrated to a volume of 85 ml. and cooled overnight. The precipitated white crystals were washed with carbon tetrachloride and dried in a vacuum desiccator at room temperature; yield, 27.3 g., m. p. 149°, green melt with decomposition. One recrystallization from carbon tetrachloride yielded small white crystals, m. p. 149.5°.

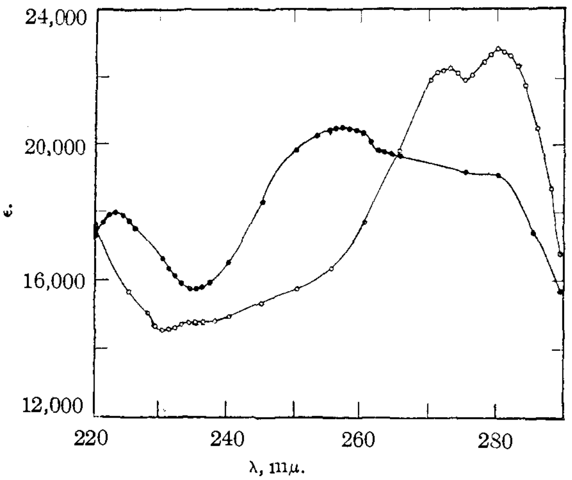


Fig. 1.—Ultraviolet absorption spectra of 3,4-bis-(*p*-propionoxyphenyl)-hexatriene-1,3,5, -○-; 3,4-bis-(*p*-hydroxyphenyl)-hexatriene-1,3,5, -●-.

Anal. Calcd. for $C_{24}H_{26}O_4Br_2$: C, 53.54; H, 4.97; Br, 29.71. Found: C, 53.48; H, 5.10; Br, 30.32.

3,4-bis-(*p*-Propionoxyphenyl)-hexatriene-1,3,5.—Twenty-one and eight-tenths grams of the above dibromo compound was heated at 150–160° for ten minutes with 220 ml. of diethylaniline. The solution darkened considerably and then was cooled to room temperature, after which it was acidified with concentrated hydrochloric acid and extracted three times with 250-ml. portions of ether. The combined ether extracts were washed with water until neutral, dried over sodium sulfate, and concentrated to a volume of 75 ml. This was then cooled to −50°, filtered and washed with a small amount of cold ether. The seven and one-tenth grams of crude crystals (m. p. 128–132°) after recrystallization from 150 ml. of petroleum ether yielded 5.4 g. of long, white needles, m. p. 134–136°.

Anal. Calcd. for $C_{24}H_{24}O_4$: C, 76.58; H, 6.43. Found: C, 76.70; H, 6.59.

When treated with bromide–bromate reagent, the triene dipropionate took up 3.84 atoms of bromine.

3,4-bis-(*p*-Hydroxyphenyl)-hexatriene-1,3,5.—Two grams of the dipropionate was refluxed for twenty minutes with 65 ml. of 10% potassium hydroxide in methanol. After this time, three volumes of water was added, and the solution made slightly acid with concentrated hydrochloric acid. At this point, the free phenol which had precipitated out, was filtered off and crystallized from ether–petroleum ether yielding 1.3 g. of slightly yellowish crystals, m. p. 196–198°. After recrystallization from aqueous isopropanol, 0.8 g. of white needles was obtained, m. p. 202–203°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.82; H, 6.11. Found: C, 81.70; H, 6.14.

Absorption Spectra.—The spectra were determined with a Beckman quartz spectrophotometer, density readings being made at 5 mμ intervals, except when in the region of maxima or minima when the readings were made at 1 mμ intervals.

The solvent used for both curves was 99% isopropanol (Carbide & Carbon). This solvent was not purified in any way since readings could be obtained when the wave length was as low as 217 mμ.

The concentration of the conjugated dipropionate was 7 mg. per liter and that of the free phenol was 7.6 mg. per liter, and the thickness of the silica absorption cells was 1.000 ± 0.002 cm.

VITAMINS, INC.
CHICAGO, ILLINOIS RECEIVED SEPTEMBER 2, 1947