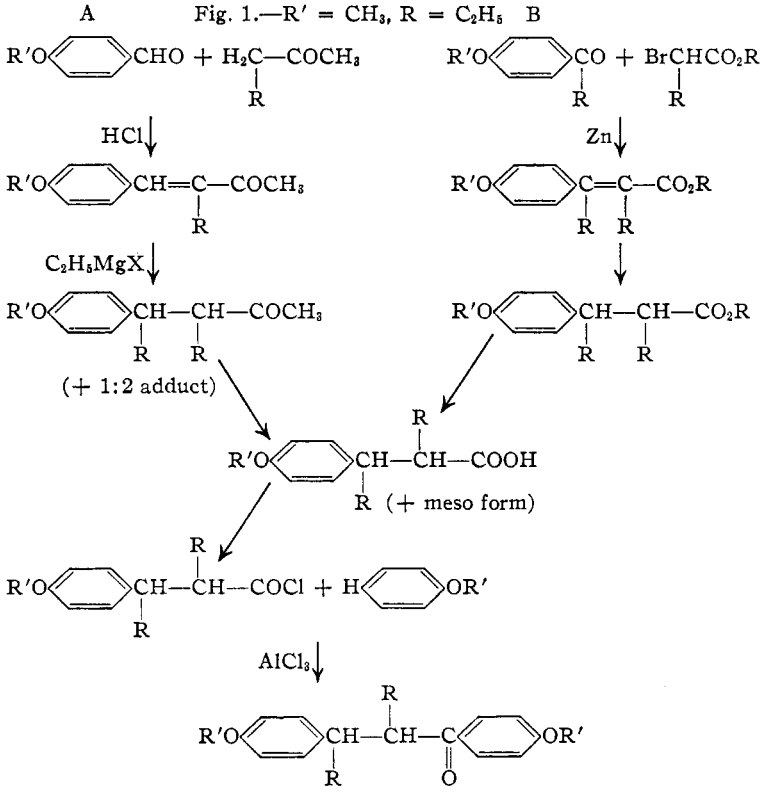
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF NEW YORK UNIVERSITY AND SCHIEFFELIN & CO., NEW YORK]

A New Synthesis of Benzestrol[1]

BY A. J. SHUKIS[2] WITH JOHN J. RITTER

During the course of research on the separation of the diastereoisomers and optical antipodes of benzestrol,[3,4] 2,4-di-(*p*-hydroxyphenyl)-3-ethylhexane, it was desired to substantiate the structure advanced for benzestrol as well as provide an intermediate structure containing a reactive functional group for resolution study.

Fig. 1.—R′ = CH_3, R = C_2H_5



1,3-Dianisyl-2-ethylpentanone-1

This has been accomplished as shown in the flow sheet in Fig. 1. The key compound is the racemic form of α-ethyl-β-anisylvaleric acid.

The compound can be prepared by either route A or B. In the former case the Bogert and Davidson[5] synthesis of alkylcinnamic acids has been extended to the *p*-methoxydihydro acids as shown. In the latter instance the procedure of Linnell and Shaikmahamud[6] has been followed except that the halo ethyl ester has been used in place of the propyl and the synthesis carried on beyond the corresponding cinnamic acid to the dihydro form.

Rubin[7] and co-workers have prepared the α-ethyl-β-anisylvaleric acid by a different route. We have found it expedient to follow the procedures outlined above.

The 1,3-dianisyl-2-ethylpentanone-1 prepared as shown in Fig. 1 gave no depression when a mixed melting point determination was carried out using the material obtained in the conventional synthesis.[4] The two products were identical. Benzestrol follows from the ketone by treatment with methyl Grignard, reduction of the resultant hexene and hydrolysis of the ether.[4] Hence on this basis the structure of benzestrol has been substantiated as being a substituted 1,3-di-(*p*-hydroxyphenyl)-propane derivative.

Experimental

α-Ethyl-*p*-methoxystyryl Methyl Ketone.—The procedure of Bogert and Davidson[5] was followed for the synthesis of the styryl ketone using anisaldehyde and methyl propyl ketone. The product distilled at 192° at 23 mm., $n^{20}D$ 1.5883-1.5893. Redistilled at 1-2 mm. the product boiled at 132-137°, $n^{20}D$ 1.5890, yield 75%. Semicarbazone m. p. 210°, reported[8] 214°.

3-Ethyl-4-anisylhexanone-2.—To a stirred Grignard solution prepared from 90 g. (0.75 mole plus 10% excess) of ethyl bromide, 18.2 g. (0.75 mole) of magnesium, and 700 ml. of anhydrous ether, a solution of 51 g. (0.25 mole) of α-ethyl-*p*-methoxystyryl methyl ketone in 200 ml. of dry ether was added dropwise, the inner temperature kept at −10°. When all the styryl ketone had been added the mixture was stirred for an hour at −10°. The solution was poured on 800 g. of crushed ice containing 200 ml. of concd. hydrochloric acid. The product was extracted with ether, the solution washed with an aqueous solution of sodium carbonate and thiosulfate. Removal of the ether and distillation of the oil gave 57 g. of a product boiling at 124-126° at 1 mm., $n^{20}D$ 1.5340, 97% yield; 2,4-dinitrophenylhydrazone m. p. 154°. The oil contained some of the olefin formed by the 1,2 addition of the Grignard, evidenced by the decolorization of 0.5% aqueous potassium permanganate and the uptake of bromine in carbon tetrachloride.

α-Ethyl-β-anisylvaleric Acid.—To 23.4 g. (0.1 mole) of 3-ethyl-4-anisylhexanone-2 dissolved in 200 ml. of ethanol, chilled, was added, with stirring, a solution of 40 g. of sodium hydroxide (1.0 mole) in 100 ml. of water to which 21.3 g. (0.3 mole) of chlorine had been added at 0°. The

(1) Abstracted from a portion of the thesis submitted to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) Stuart, Shukis and Tallman, THIS JOURNAL, **67**, 1475 (1945).

(4) Stuart, Shukis, Tallman, McCann and Treves, *ibid.*, **68**, 729 (1946).

(5) Bogert and Davidson, *ibid.*, **54**, 334 (1932).

(6) Linnell and Shaikmahamud, *Quart. J. Pharm. Pharmacol.*, **14**, 64 (1941).

(7) Rubin, *et al.*, THIS JOURNAL, **66**, 2075 (1944); **67**, 193 (1945).

(8) Gheorghin, *Bull. soc. chim.*, **53**, 1442 (1933).

temperature of the reaction was kept at 20°, requiring fifteen minutes for the addition, stirred for an additional hour. At this stage two layers were present as well as some solid salt. The mixture was distilled to remove the chloroform formed and the alcohol. On cooling, the sodium salt of the α-ethyl-β-anisylvaleric acid solidified. Dissolved in water, clarified with Norite, followed by hydrochloric acid acidification gave 5 g. of a light tan solid melting at 125°, a 21% yield. Recrystallized from 75% acetic acid, aqueous alcohol or petroleum ether (40–60°) the racemic form melted at 135–136°. The amide melted at 139–142°.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; neut. equiv., 236.3. Found: C, 70.93; H, 8.66; neut. equiv., 237.6.

The *meso*-form was isolated from the mother liquors as a liquid.

Ethyl (α-β-Diethyl-*p*-methoxy)-cinnamate.—To a stirred mixture of 17.3 g. (0.105 mole) of *p*-methoxypropiophenone, 30 ml. each of benzene and toluene, 7 g. (0.107 mole) of zinc dust, 21 g. (0.108 mole) of ethyl α-bromobutyrate was added dropwise. An iodine crystal aided in starting the reaction. The ester completely added, the mixture was refluxed and stirred for an hour. Poured into 100 ml. of cold 20% sulfuric acid the benzene-toluene layer was separated, washed with water, dilute sodium carbonate solution, water. Removal of the solvents and distillation of the oil gave 21.3 g. of product boiling at 124–126° at 0.3 mm., $n^{20}D$ 1.5174, 86% yield.

Ethyl (2-Ethyl-3-anisyl)-valerate.—Some 13.2 g. (0.05 mole) of the ethyl (α,β-diethyl-*p*-methoxy)-cinnamate was reduced in 75 ml. of ethanol in the Parr hydrogenator at 60 lb. hydrogen pressure over 0.1 g. of platinum oxide and 0.1 g. of palladium black. The hydrogen uptake was complete in four hours. The catalyst was filtered off, the alcohol removed, distillation of the oil at 0.8 mm. gave 12.9 g. boiling at 122°, $n^{20}D$ 1.4935, 97% yield.

α-Ethyl-β-anisylvaleric Acid.—Saponification of the ethyl (2-ethyl-3-anisyl)-valerate with methanolic alkali gave the racemic acid melting at 133° after recrystallization from aqueous methanol. Recrystallized from petroleum ether (40–60°) the acid melted at 135–137°, yield 42%. A mixed melting point with the acid obtained by the synthesis from the *p*-methoxystyryl methyl ketone gave no depression. The products were identical.

Reaction of α-Ethyl-β-anisylvaleryl Chloride with Anisole.—Four grams (0.0169 mole) of the α-ethyl-β-anisylvaleric acid was warmed with 10 ml. of thionyl chloride under reflux for an hour. The excess thionyl chloride was removed under reduced pressure. To the residue was added 10 ml. of ethylene dichloride followed by 8.4 g. (0.063 mole) of aluminum chloride. The mixture was chilled and 4 g. (0.037 mole) of anisole added dropwise. After three hours the mixture was poured into 100 g. of crushed ice containing 10 ml. of concd. hydrochloric acid. Extracted with benzene, washed with water, dilute sodium carbonate solution, dried, distilled at 4–5 mm., 3.1 g. of material boiling at 190–194°, 61% yield, was obtained. Recrystallized twice from methanol after a Norite treatment, the solid melted at 81–82°. A mixed melting point determination with the solid ketone prepared from *p*-methoxybutyrophenone[4] gave no depression. The products were identical.

Summary

A new and independent synthesis from α-ethyl-β-anisylvaleric acid substantiates the structure of benzestrol[4] as a 1,2,3-tri-alkyl substituted 1,3-di-(*p*-hydroxyphenyl)-propane derivative.

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The Synthesis of a Geometrical Isomer of Pellitorine[1,2]

BY MARTIN JACOBSON

Pellitorine, isolated from the roots of *Anacyclus pyrethrum* DC.,[3] has previously been shown[3,4] to be N-isobutyl-2,6-decadienamide (VIII). In view of the insecticidal activity of this compound,[4] its synthesis was attempted in this laboratory.

The steps employed in this synthesis are shown in the accompanying chart. Dihydropyran (I) was chlorinated, to give 2,3-dichlorotetrahydropyran (II) in 91% yield, by a slight modification of the method of Paul.[5] Treatment of II with *n*-propylmagnesium bromide gave a 73% yield of 3-chloro-2-*n*-propyltetrahydropyran (III). Treatment of III with sodium split the ring to give 4-octen-1-ol (IV) in 86% yield, a general procedure previously used to obtain 4-penten-1-ol[6] and 4-nonen-1-ol.[5,7] Dichromate oxidation of the unsaturated alcohol (IV) by the low-temperature method of Delaby and Guillot-Allègre[8] resulted in a 35% yield of 4-octene-1-al (V). Treatment of the aldehyde (V) with malonic acid in pyridine with piperidine as catalyst (Doebner reaction) gave the acid fragment of pellitorine (2,6-decadienoic acid) (VI) in 17% yield. The acid chloride (VII) was prepared in 96% yield by use of thionyl chloride in low-boiling petroleum ether, and addition of VII to isobutylamine in ether solution yielded 95% of N-isobutyl-2,5-decadienamide (VIII).

There are four possible *cis* and *trans* isomers having structure VIII, namely, *cis–cis*, *cis–trans*, *trans–cis*, and *trans–trans*. The compound synthesized by the procedure described above, although showing approximately the same boiling point (150° at 0.1 mm.) as natural pellitorine (155–165° at 0.3–0.5 mm.),[4] melted at 54–55°, whereas the natural isomer melts at 72°.[9] Both materials are

(1) Report of a study made under the Research and Marketing Act of 1946. Article not copyrighted.

(2) Presented before the Division of Organic Chemistry, at the Atlantic City Meeting of the American Chemical Society, September 21, 1949.

(3) Gulland and Hopton, *J. Chem. Soc.*, 6 (1930).

(4) Jacobson, THIS JOURNAL, **71**, 366 (1949).

(5) Paul, *Compt. rend.*, **218**, 122 (1944).

(6) Paul and Normant, *Bull. soc. chim.*, [5] **10**, 484 (1943).

(7) Paul and Riobé, *Compt. rend.*, **224**, 474 (1947).

(8) Delaby and Guillot-Allègre, *Bull. soc. chim.*, [4] **53**, 301 (1933).

(9) After this paper was submitted for publication, the synthesis of the *cis–cis* and *cis–trans* isomer of pellitorine, was reported by Raphael and Sondheimer (*Nature*, **164**, 707 (1949)) and by Crombie and Harper (*ibid.*, **164**, 1053 (1949)), respectively. These isomers are identical with neither the natural product nor our solid isomer and indications point to the latter as being the *trans–trans* isomer.