113. *An Alternative Route to Stilboestrol.*

A. E. Wilder Smith.

An alternative route to stilboestrol using *n*-butyric acid and *p*-bromoanisole as starting materials is described.

The original synthesis of stilboestrol described by Dodds, Golberg, Lawson, and Robinson (*Proc. Roy. Soc.*, 1939, B, **127**, 140) was carried out from anisaldehyde as starting material, *via* α-ethyldeoxyanisoin and 3 : 4-dianisylhexane-3-ol, followed by dehydration and demethylation.

Many attempts have been made to improve on this synthesis of which account is given by Jones (*Ann. Reports*, 1943, **40**, 137). More recently Wilds and Biggerstaff (*J. Amer. Chem. Soc.*, 1945, **67**, 789) have reported a synthesis of stilboestrol from α-(*p*-methoxyphenyl)-*n*-butyric acid and anisole. Here, as in the original synthesis, α-ethyldeoxyanisoin is the key intermediate. The α-(*p*-methoxyphenyl)-*n*-butyric acid was prepared by nitration, reduction, and deamination of α-phenyl-*n*-butyric acid, so that the preparation involves a rather long series of intermediates. A further recent synthesis is reported by Rubin, Kozlowski, and Salmon (*J. Amer. Chem. Soc.*, 1945, **67**, 192) who used anisaldehyde cyanohydrin as starting material. Additional references to the subject are given in their paper.

A number of the reported routes to stilboestrol use, as the key intermediate, α-ethyldeoxyanisoin, so that a short and easy route to this substance would provide at the same time a convenient route to stilboestrol. The method of synthesis described in this communication is an extension of that used by Tiffeneau and his

collaborators (*e.g.*, *Bull. Soc. chim.*, 1931, **49**, 1758), McKenzie and his collaborators (*e.g.*, *J.*, 1926, 779; 1925, 283; 1924, 2105), and Mills and Smith (unpublished work) for the preparation of deoxybenzoins.

It has been found that ethyl α-amino-*n*-butyrate hydrochloride reacts with *p*-anisylmagnesium bromide to give β-amino-αα-dianisyl-*n*-butanol in good yield. This amino-alcohol on deamination gives the required α-ethyldeoxyanisoin, also in good yield.

$$HCl,NH_2\cdot CHEt\cdot CO_2Et \xrightarrow{MeO\cdot C_6H_4\cdot MgBr} NH_2\cdot CHEt\cdot C(OH)(C_6H_4\cdot OMe)_2 \xrightarrow{HNO_2}$$

$$CHEt(C_6H_4\cdot OMe)\cdot CO\cdot C_6H_4\cdot OMe \xrightarrow{3\ Stages} CEt(C_6H_4\cdot OH):CEt\cdot C_6H_4\cdot OH$$

Owing to the lower reactivity of the *p*-anisyl compared with the phenyl Grignard reagent (McKenzie *et al.*, *loc. cit.*) the reaction with the amino-ester hydrochloride does not proceed to completion so rapidly in boiling ether; replacement of ether by benzene as solvent, followed by refluxing for 24 hours, gives slightly better yields. The further stages of the synthesis of stilboestrol from ethyl deoxyanisoin proceeded as reported by Dodds *et al.* (*loc. cit.*) and by Wilds and Biggerstaff (*loc. cit.*).

It will readily be seen that, by variations of the substituents in the Grignard reagent used in the reaction on the amino-ester hydrochloride, the corresponding ring-substituted stilboestrols may be obtained. Similarly, by using the appropriate amino-acid, the substituents on the stilbene ethylenic carbon atoms likewise may be varied.

Experimental.

(M. ps. and b. ps. are uncorrected. The analyses are by Drs. Weiler and Strauss, Oxford.)

α-Amino-n-butyric Acid.—This was prepared by bromination of *n*-butyric acid (78% yield) followed by amination with strong aqueous ammonia (65% yield) according to the method of Abderhalden and Chang (*Z. physiol. Chem.*, 1912, **77**, 475). Esterification was carried out by suspension in absolute ethanol and passage of dry hydrogen chloride until solution was effected. Repetition of the process after removal of the alcohol gave the solid, somewhat hygroscopic ester hydrochloride.

Action of p-Anisylmagnesium Bromide on Ethyl α-Amino-n-butyrate Hydrochloride.—To the Grignard reagent prepared from magnesium (1·5 g.) and *p*-bromoanisole (11·22 g., 6 mols.) in dry ether (150 ml.) was added ethyl α-amino-*n*-butyrate hydrochloride (1·68 g., 1 mol.). The ether was then removed by distillation and replaced by an equal volume of dry benzene and the solution refluxed for 24 hours. After decomposition with crushed ice and dilute hydrochloric acid, the ether layer was separated and washed with water; the combined aqueous layers were then extracted once with fresh ether and the ether layers discarded. The aqueous layer was made alkaline with ammonia after adding excess of solid ammonium chloride, and extracted four times with ether; the combined ether layers were dried (Na_2SO_4) and then treated with dry hydrogen chloride until the solution was faint pink. After being kept at 0° overnight the pale yellow crystals of β-amino-αα-dianisyl-*n*-butanol hydrochloride were filtered off. Yield, 2·15 g. (64%). Slightly reduced yields were obtained when ether was used instead of benzene. After purification by solution in water, making alkaline with 2N-sodium hydroxide, extraction with ether, and reprecipitation from the dry ether solution by dry hydrogen chloride, the hydrochloride was recrystallised three times from absolute ethanol–light petroleum (b. p. 60—80°) and thus obtained as fine pale yellow needles, m. p. 198—199° (decomp.) (Found: C, 63·9; H, 7·2; N, 4·14; equiv. wt., 334. Calc. for $C_{18}H_{24}O_3NCl$: C, 64·1; H, 7·1; N, 4·16%; equiv. wt., 337·9).

Conversion of β-Amino-αα-dianisyl-n-butanol Hydrochloride into the Free Base.—The hydrochloride (11·7 g.) was dissolved in warm water (300 ml.) and extracted once with ether; the ether layer was separated and discarded. After making the aqueous layer just alkaline with ammonia, alcohol was added in just sufficient quantity to dissolve the precipitated oil when hot and the solution was then set aside to crystallise. To induce crystallisation it was usually necessary to seed with crystals obtained originally by keeping a solution for several weeks at 0°. Yield, 9·6 g. (92%). Several crystallisations from ethanol yielded shining flat white needles, m. p. 85—86° (Found: C, 72·0; H, 7·9; N, 4·65. Calc. for $C_{18}H_{23}O_3N$: C, 71·7; H, 7·7; N, 4·65%).

Deamination of β-Amino-αα-dianisyl-n-butanol.—The amino-alcohol (4·7 g.) was dissolved in 25% acetic acid (50 ml.) and cooled to 0°. Sodium nitrite (1·2 g.) in water (10 ml.) at 0° was added with agitation. After a few minutes an oil was precipitated. After being kept for 4 hours at room temperature the solution was neutralised with a slight excess of solid sodium bicarbonate, extracted three times with ether, and the combined ether layers were dried (Na_2SO_4). Removal of the ether gave 4·36 g. (98% of theory) of a golden oil which, on distillation, yielded a main fraction, b. p. 177—182°/0·2 mm., 4·02 g. (90% of theory). This α-ethyldeoxyanisoin was obtained crystalline according to the method of Wilds and Biggerstaff (*loc. cit.*), and after three crystallisations from light petroleum (b. p. 60—80°) and benzene melted at 46—48° to a cloudy liquid, clearing at 50—53° (Found: C, 75·9; H, 7·3. Calc. for $C_{18}H_{20}O_3$: C, 76·0; H, 7·1%).

I am indebted to the Council of the Middlesex Hospital Medical School for the provision of laboratory facilities for this work, which was carried out during the tenure of the Countess of Lisburne Memorial Fellowship.

S. A. Courtauld Institute of Biochemistry,
Middlesex Hospital, London, W. 1.

[*Received, January 12th*, 1946.]