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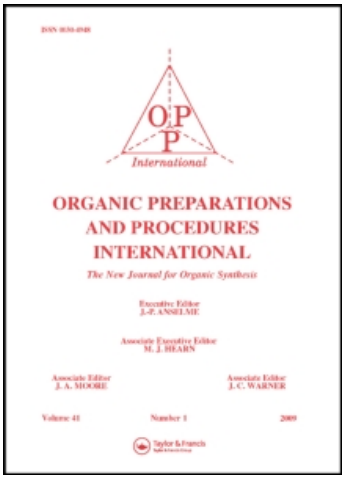

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SYNTHESIS OF α-AMINO-β-(*p*-HYDR0XYPHENOXY) PROPIONAMIDE HYDROCHLORIDE

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SYNTHESIS OF α-AMINO-β-(p-HYDROXYPHENOXY)PROPIONAMIDE HYDROCHLORIDE

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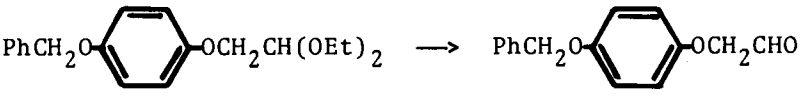
In a continuation of a program to synthesize various derivatives of serine for anti-thyroid agent screening[2] α-amino-β-(p-hydroxyphenoxy)propionamide hydrochloride(5) has been synthesized from (p-benzyloxyphenoxy)acetaldehyde diethyl acetal(1).



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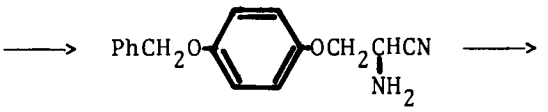

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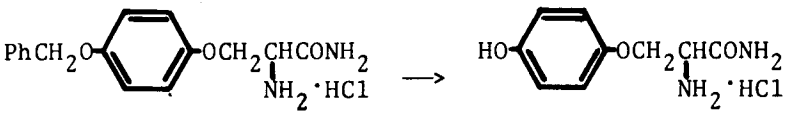

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Acid hydrolysis of 1 gave the aldehyde 2 which was converted to the aminonitrile 3 by the Strecker reaction or by treatment with ammonium carbonate and potassium cyanide in ethanol at 50-60°; the latter reaction at higher temperatures gave p-benzyloxyphenol. Hydrolysis of the nitrile 3 with hydrochloric acid in dioxane at room temperature gave the amide 4 which was cleaved by catalytic hydrogenation to α-amino-β-(p-hydroxyphenoxy)propionamide hydrochloride(5).

Further hydrolysis of the amide(4) by acid or base to the amino acid was not successful; p-benzyloxyphenol and intractable tars were the main products. These results indicate that the β-phenoxyalanine structure is sensitive to acid and base and undergoes a retro addition of phenol and forms α-aminoacrylamide or α-aminoacrylic acid which polymerize.

Iodination of the amide 5 with either iodine and various oxidizing agents, potassium triiodide and base, or iodine monochloride alone either did not occur or gave tars.

EXPERIMENTAL

Melting points and the boiling point are not corrected. Infrared spectra were determined with a Perkin-Elmer Model 21 Spectrophotometer using Nujol mulls.

(p-Benzyloxyphenoxy)acetaldehyde Diethyl Acetal(1). A solution of sodium (4.7g) in diethylene glycol (170ml) was treated with p-benzyloxyphenol (40g) and chloroacetaldehyde diethyl acetal (31g) and the resulting mixture was heated with stirring at 140° for 6 hrs. After cooling the mixture

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was poured into water (100ml) and extracted with four 150ml portions of ether. The ether extract was washed with 6N sodium hydroxide until no color was generated in the basic layer, then with water and dried (Na_2SO_4). Upon removal of the solvent a dark oil was obtained and distilled to yield 18g (28%) of a colorless liquid, b.p. 200-210°/3-4mm; n_D^{25} 1.6730. The use[3] of potassium hydroxide as a base in this reaction gave only starting material.

(p-Benzyloxyphenoxy)acetaldehyde(2). (p-Benzyloxyphenoxy)-acetaldehyde diethyl acetal(1) (35g) was refluxed with 2N sulfuric acid (100ml) for 2 hours. The aldehyde(2) obtained upon cooling was recrystallized from heptane until the infrared spectrum showed no hydroxyl absorption; yield, 11.3g (42%), mp. 74-75°; IR 1765-1770cm^{-1}(CO).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.33; H, 5.86.

The 2,4-dinitrophenylhydrazone melted at 144-145°.

Anal. Calcd for $C_{21}H_{18}O_6N_4$: C, 59.71; H, 4.29; N, 13.26. Found: C, 59.97; H, 4.44; N, 13.18.

α-Amino-β-(p-benzyloxyphenoxy)propionitrile(3). A. A solution of ammonium hydroxide (25ml) was treated with absolute ethanol (200ml) saturated with ammonia and (p-benzyloxyphenoxy)acetaldehyde (1.64g) in absolute ethanol (250ml). The resulting solution was allowed to stand for 3 days at room temperature and upon partial removal of the

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solvent at reduced pressure 1.20g (66%) of white crystals of the pure aminonitrile 3, mp. 121-22° was obtained. Further recrystallization from either 50% ethanol or heptane did not change the melting point; IR 3000-3300cm^{-1}(NH).

Anal. Calcd for $C_{16}H_{16}O_2N_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.76; H, 5.91; N, 10.22.

B. A solution of the aldehyde(2) (3.0g) in 95% ethanol (200ml) was added to a solution of potassium cyanide (1.21g) and ammonium carbonate (3.60g) in water (150ml) and the resulting solution was heated at 50-60° for 2 hrs. Upon cooling 1.58g (48%) of the aminonitrile(3) was obtained.

α-Amino-β-(p-benzyloxyphenoxy)propionamide Hydrochloride(4). A solution of the aminonitrile(3) (1.62g) in dioxane (30ml) was treated with concentrated hydrochloric acid (30ml) and allowed to stand at room temperature for 24 hrs. The solid which had precipitated gave upon recrystallization from aqueous ethanol 1.27g (65%) of white crystals, mp. 218-219° (dec.); IR (Nujol) 1690-1710(CO), 1220-1250cm^{-1}(-O-).

Anal. Calcd for $C_{16}H_{19}O_3N_2Cl$: C, 59.53; H, 5.96; N, 8.67. Found: C, 59.35; H, 5.96; N, 8.58.

α-Amino-β-(p-hydroxypenoxy)propionamide Hydrochloride(5). A solution of the propionamide hydrochloride(4), (0.76g) in 80% ethanol (50ml) was hydrogenated at 30 psi for 3 hrs in the presence of 10% palladium on charcoal catalyst (0.06g).

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α-AMINO-β-(p-HYDROXYPHENOXY)PROPIONAMIDE HYDROCHLORIDE

Removal of the catalyst and solvent gave a solid (0.45g) which was purified by dissolution in 95% ethanol and precipitation with the addition of ethyl acetate to 0.24g (44%), mp. 199-201°; IR (Nujol) 1700-1710(CO), 1200-1240cm^{-1}(-O-).

Anal. Calcd for $C_9H_{13}O_3N_2Cl$: C, 46.45; H, 5.63; N, 12.04. Found: C, 46.52; H, 5.51; N, 12.01.

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