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Synthesis of 2,4,5-Trihydroxyphenylpropylamine

Short Communication

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Condensation of 2,4,5-tribenzyloxybenzaldehyde with α-cyanoacetic acid gave 2,4,5-tribenzyloxyphenyl-α-cyanoacrylic acid which on decarboxylation gave 2,4,5-tribenzyloxyphenylacrylonitrile. Stepwise reduction of the double bond with sodium amalgam and then the cyano group with diborane followed by catalytic hydrogenolysis afforded 2,4,5-trihydroxyphenylpropylamine.

(Keywords: Sodium amalgam reduction; 2,4,5-Tribenzyloxybenzaldehyde; 2,4,5-Trihydroxyphenylpropylamine)

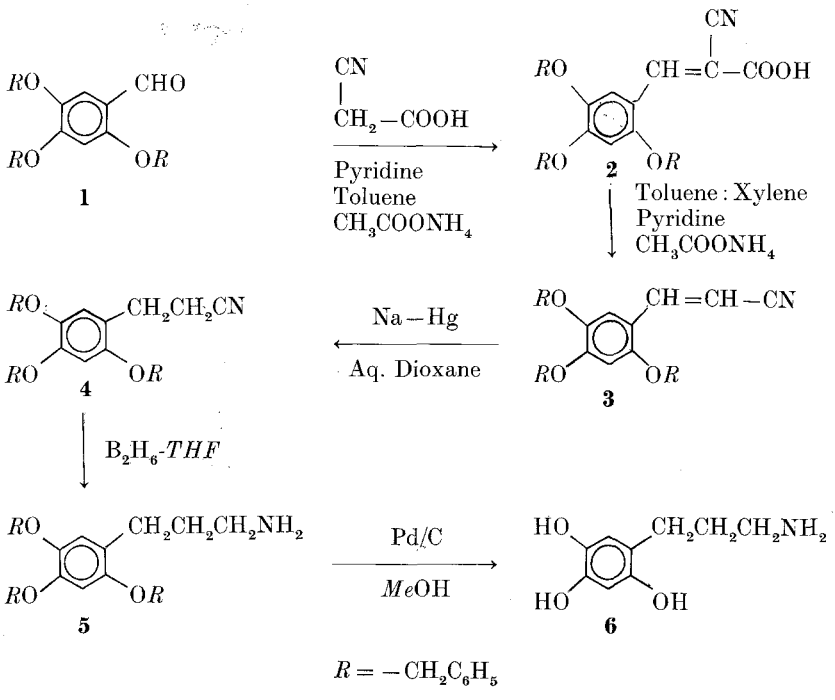
Synthese von 2,4,5-Trihydroxyphenylpropylamin
(Kurze Mitteilung)

Die Kondensation von 2,4,5-Tribenzyloxybenzaldehyd mit α-Cyanessigsäure ergab 2,4,5-Tribenzyloxyphenyl-α-cyanacrylsäure; diese ergab nach Decarboxylierung 2,4,5-Tribenzyloxyphenylacrylnitril. Stufenweise Reduktion der Doppelbindung mit Natriumamalgam und dann der Cyano-Gruppe mit Diboran gefolgt von katalytischer Hydrogenolyse führte zu 2,4,5-Trihydroxyphenylpropylamin.

As a part of ongoing program for the synthesis of neuropharmacological compounds[1], the preparation of 2,4,5-trihydroxyphenylpropylamine was undertaken.

2,4,5-Tribenzyloxybenzaldehyde (**1**), required as the starting material in this synthesis was made according to the literature method[2]. Base catalysed condensation[3] of cyanoacetic acid and 2,4,5-tribenzyloxybenzaldehyde (**1**) furnished 2,4,5-tribenzyloxyphenyl-α-cyanoacrylic acid (**2**). Decarboxylation was effected by refluxing **2** in a mixture of toluene: xylene (1 : 1), pyridine and ammonium acetate for 6 days to yield 2,4,5-tribenzyloxyphenylacrylonitrile (**3**). Catalytic reduction of **3** over *Raney* nickel[3b] or reduction by lithium aluminium hydride failed to give the desired 2,4,5-tribenzyloxyphenylpropylamine **5**. It was then

considered worthwhile to carry out stepwise reduction of compound **3**. The double bond of **3** was selectively reduced by 3% sodium amalgam[4] to obtain 2,4,5-tribenzyloxyphenylpropionitrile (**4**) in good yield without effecting the cyano group. Next, the cyano group of **4** was subjected to diborane reduction[5] to obtain **5** which underwent hydrogenolysis[6] on 10% palladium-carbon to yield 2,4,5-trihydroxyphenylpropylamine (**6**).



Experimental

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 337 instrument in KBr. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

2,4,5-Tribenzyloxyphenyl-α-cyanoacrylic Acid (**2**)

In a three necked flask equipped with a mechanical stirrer and *Dean-Stark* water trap were placed 2,4,5-tribenzyloxybenzaldehyde (**1**) (106 g, 0.25 mol), cyanoacetic acid (21.3 g, 0.25 mol), toluene (500 ml), pyridine (55 ml) and ammonium acetate (3 g). The mixture was refluxed with stirring for 1 h and allowed to cool. The precipitate was filtered and dried to give 128 g of orange solid, m.p. 160–164°. This intermediate was used without further purification for the second step. A small portion of the crude product was washed with water,

dried and recrystallized from methanol, m.p. 196–197°; IR (KBr), 2220 cm^{-1} (conjugated —CN). Anal. Calcd. for $C_{31}H_{25}NO_5$: C 75.75, H 5.13, N 2.85. Found: C 75.47, H 5.05, N 2.81.

2,4,5-Tribenzyloxyphenylacrylonitrile (**3**)

A mixture of crude **2** (90 g), toluene : xylene (1 : 1; 500 ml), pyridine (50 ml), and ammonium acetate (3 g) was stirred under reflux for 6 days. The reaction mixture was cooled and filtered to remove some unreacted starting material. The filtrate was concentrated to dryness under reduced pressure. The crude solid was washed with aqueous sodium carbonate, water, and dried. Recrystallization from alcohol gave product (9 g), m.p. 139–141°. An analytical sample was crystallized from alcohol, m.p. 145–146°; IR (KBr), 2220 cm^{-1} (conjugated —CN). Anal. Calcd. for $C_{30}H_{25}NO_3$: C 80.51, H 5.63, N 3.13. Found: C 80.61, H 5.68, N 3.02.

2,4,5-Tribenzyloxyphenylpropionitrile (**4**)

To a solution of **3** (4.3 g, 0.0096 mol) in a dioxane (50 ml) and water (5 ml) was added 3% sodium-amalgam (100 g) in small portions over a 4 h period. The mixture was further stirred at room temperature for 16 h. The organic layer was carefully decanted and evaporated to dryness under reduced pressure. The oily product was washed with water and the water layer was removed by decantation. Recrystallization of the crude product from alcohol gave 3.2 g (74.1%) of crystalline solid, m.p. 101–103°; IR (KBr), 2250 cm^{-1} (—CN). Anal. Calcd. for $C_{30}H_{27}NO_3$: C 80.15, H 6.05, N 3.12. Found: C 79.87, H 6.04, N 2.97.

2,4,5-Tribenzyloxyphenylpropylamine Hydrogen Oxalate (**5**)

To a stired solution of **4** (2 g, 0.0044 mol) in dry tetrahydrofuran (56 ml) was added dropwise over a 30 min 1 *M* boranetetrahydrofuran complex (Aldrich) (56 ml), at room temperature. The solution was further stirred for 16 h and was carefully treated with dilute hydrochloric acid (rather violent). The reaction mixture was stirred at room temperature for 1 h and concentrated to dryness under reduced pressure. The resulting product was treated with aqueous sodium hydroxide ($pH \sim 11$–12) and extracted with ether (3 × 150 ml). The ether solution was dried over magnesium sulfate and filtered. The solvent was removed by distillation under reduced pressure. The product thus obtained was dissolved in alcohol (8 ml) and to the stirred solution was added oxalic acid solution (0.34 g, 0.0038 mol in 5 ml alcohol). The crystalline hydrogen oxalate was filtered, washed with small amount of ice-cold ethanol and dried to yield 1.5 g (62%) of product. M.p. 155–157°. Anal. Calcd. for $C_{30}H_{31}NO_3 \cdot C_2H_2O_4$: C 70.70, H 6.12, N 2.58. Found: C 70.94, H 6.11, N 2.48.

2,4,5-Trihydroxyphenylpropylamine Creatinine Sulfate (**6**)

A mixture of **5** (1.2 g, 0.0022 mol), methanol (200 ml), and 10% Pd-C (0.60 g) was subjected to hydrogenolysis in a *Parr* apparatus (30 psi). After 10 h the catalyst was removed by filtration and to the filtrate was added sulfur dioxide treated methanol (25 ml) and the solvent was evaporated under reduced pressure to yield a semi-solid. It was dissolved in 1 *N* sulfuric acid (4.4 ml) and creatinine (0.26 g, 0.0023 mol) was added as a solid. To this solution was added acetone to the cloud point ($\sim$ 60 ml) and the product slowly crystallized in two crops, 0.36 g of solid was triturated with acetone ($\sim$ 3 ml containing 6 drops of water) to yield

0.2 g (22.7%) of product, m.p. 221–223° (decomp.). Anal. Calcd. for $C_9H_{13}NO_3 \cdot C_4H_7N_3O \cdot {}^1/_4 H_2O$: C 39.14, H 5.69, N 14.06. Found: C 39.17, H 5.60, N 14.51.

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