Syntheses of *p*-Dimethylaminobenzyl Alcohol and Esters of its Methiodide

LARS-ERIK TAMMELIN

Research Institute of National Defence, Dept. 1, Sundbyberg 4, Sweden

p-Dimethylaminobenzyl alcohol has been synthesized by catalytic hydrogenation of the corresponding aldehyde. Methiodides of the *p*-dimethylaminobenzyl alcohol and esters from acetic-, malonic-, succinic-, glutaric- and adipic acids have been prepared. The conditions for methylation of *p*-dimethylaminobenzyl alcohol are discussed. The esters of *p*-trimethylammoniumbenzyl alcohol have been shown to have neuromuscular blocking effects.

p-Dimethylaminobenzyl alcohol has been synthesized by Smith and Welch¹ who also review earlier literature in this field. The same authors² point out that *p*-dimethylaminobenzyl alcohol easily reacts, through loss of water, with phenols and aromatic amines. Reactions of this type occurring as side reactions presumably explains the difficulties of earlier authors to obtain good yields of a pure product. Smith and Welch used the action of formaldehyde on dimethylaniline. Reduction of *p*-dimethylaminobenzaldehyde has also been accomplished by electrolysis³, sodium amalgam³, lithium aluminium hydride⁴ and sodium borofluoride⁵. The latter method provides the best yield (96 %). Since no report has been found on direct catalytic hydrogenation of *p*-dimethylaminobenzaldehyde it seemed reasonable to test that method of synthesis. *p*-Trimethylammoniumbenzyl alcohol and corresponding esters can be expected to have interesting pharmacological actions because of a structural resemblance to choline and the choline esters.

SYNTHESES

p-Dimethylaminobenzyl alcohol. One mole of *p*-dimethylaminobenzaldehyde was dissolved in 160 ml of hot abs. ethanol. 1 g of PtO₂ and 2 ml of 0.1 M FeCl₃ solution were added to the alcoholic solution and the mixture treated with hydrogen at 10 kg/cm² and 50° C. The hydrogenation was considered to be complete when 1.2 moles of hydrogen were consumed. The reaction mixture was filtered and the *p*-dimethylaminobenzyl alcohol purified by fractional distillation *in vacuo*, b. p. 115–120°/1 mm Hg, *n*_D²⁰ 1.5780. Yield 50 %. For analyses see the methiodide.

p-Trimethylammoniumbenzyl alcohol. One mole of *p*-dimethylaminobenzyl alcohol and 1.1 moles of methyl iodide were mixed in 8 volume parts of ether in a glass stoppered round

bottomed flask and kept at 25° C. The precipitate formed was filtered off after 4 days and recrystallized twice from methanol, m. p. 261° and yield 60 %. (Found: C 41.3; H 5.4; I 43.4. Calc. for C₁₀H₁₂ONI (293.2): C 41.1; H 5.5; I 43.4).

p-Trimethylammoniumbenzyl ester of acetic acid. One mole of acetylchloride and 1 mole of *p*-dimethylaminobenzyl alcohol were boiled in ether for one hour. The reaction mixture was washed with 5 % aqueous sodium bicarbonate solution and dried with sodium sulfate. 1.5 moles of methyl iodide were added to the water free ether solution. After two weeks at 25° C the precipitate formed was filtered off and purified by dissolution in alcohol and reprecipitation with ether. The purified product had a m.p. 186° (decomp.) and was obtained in 33 % yield. (Found: C 43.8; H 5.5; I 38.1. Calc. on C₁₁H₁₅O₂NI (335.2): C 43.0; H 5.4; I 37.8).

p-Trimethylammoniumbenzyl esters of aliphatic dicarboxylic acids. One mole of acid dichloride (malonyl-adipyl) and 2 moles of *p*-dimethylaminobenzyl alcohol were boiled in ether for one hour. The reaction mixture was washed by 5 % aqueous sodium bicarbonate solution and dried with water free sodium sulfate. 2.5 moles of methyl iodide were added and the precipitate formed was filtered off after two weeks at 25° C, and purified by solution in alcohol and reprecipitation with ether. Yield about 30 %. For data see Table 1.

Table 1.

Ester	Formula	Molecular weight	m. p.	C		H		I	
				calc.	found	calc.	found	calc.	found
malonic	C ₂₂ H ₃₂ O ₄ N ₂ I ₂	654.3	182	42.3	42.7	4.9	5.1	38.8	38.6
succinic	C ₂₄ H ₃₄ O ₄ N ₂ I ₂	668.4	128	43.2	43.4	5.1	5.3	37.9	37.7
glutaric	C ₂₅ H ₃₆ O ₄ N ₂ I ₂	682.4	144	44.0	42.9	5.3	5.5	37.2	36.8
adipic	C ₂₆ H ₃₈ O ₄ N ₂ I ₂	696.4	147	44.9	44.3	5.5	5.5	36.4	36.1

Good yields from the catalytic hydrogenation of the *p*-dimethylaminobenzaldehyde are obtained only if the aldehyde is completely consumed. The aldehyde seems to provoke side reactions during the distillation, with diminished yield of the alcohol as a consequence. Another complication which has happened a few times is that the catalyst is poisoned during the process of hydrogenation. It is therefore recommended that the completeness of the hydrogenation is tested by the addition of new catalyst, if hydrogen consumption ceases before the calculated amount is consumed. If these possible troubles are overcome the product obtained is well in accordance with the *p*-dimethylaminobenzyl alcohol from the condensation of formaldehyde and dimethylaniline according to Smith and Welch¹ with respect to refractive index and boiling point.

The relative rapidity of the methylation of *p*-dimethylaminobenzyl alcohol gave the impulse to determine whether the *p*-trimethylammoniumbenzaldehyde could be synthesized in a similar way. However, in this case methyl iodide did not react at 25° C in ether. The phenomenon might be described in formulae as follows.

This and other resonance possibilities engage the electron pair at the nitrogen atom. In the case of the alcohol and its esters the corresponding electron pair seems to be more free and thus enables the methylation to proceed.

The present author has not isolated the *p*-dimethylaminobenzyl esters either by crystallization or by distillation *in vacuo*. The quaternary derivatives are easier to isolate but even in this case purification has its obstacles. Dissolution in alcohol and precipitation with ether, which is recommended, is not an ideal method. It does not always lead to the correct composition of the compound especially when the impurities are quaternary products. However, following the given prescriptions for the syntheses, impurities of the type mentioned above seem to have been avoided as follows from the analytical data of the final products.

The iodides of the bis-(*p*-trimethylammoniumbenzyl) esters are water soluble, crystalline, pale yellow substances. Preliminary experiments have shown that they are potent neuromuscular blocking agents and choline esterase inhibitors (although not very potent), effects which could be expected from the structural similarity to the choline esters. The pharmacological data will be published elsewhere ⁶.

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