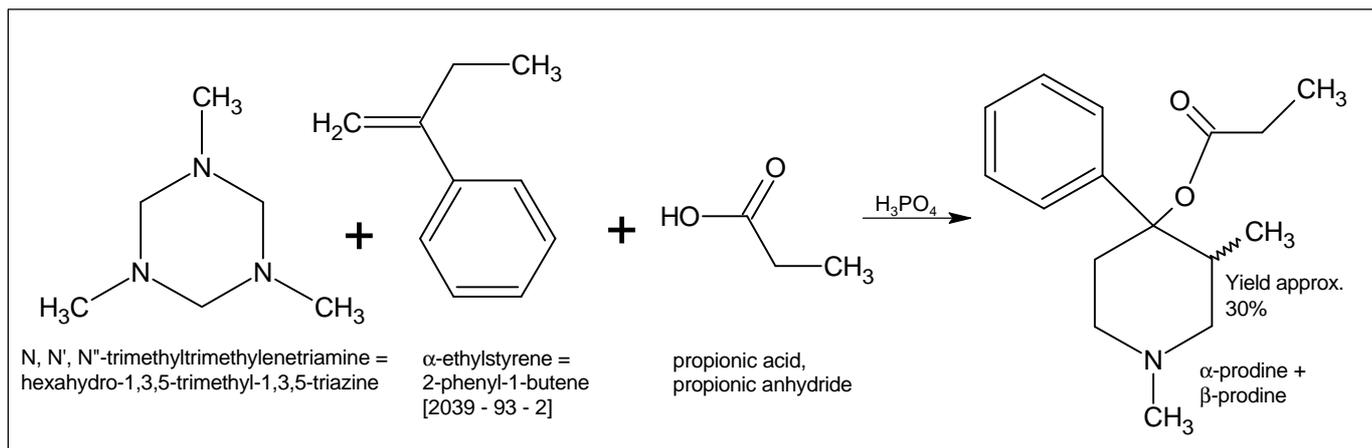


## Synthesis of $\alpha$ - and $\beta$ -Prodine according to US patent 2,765,315

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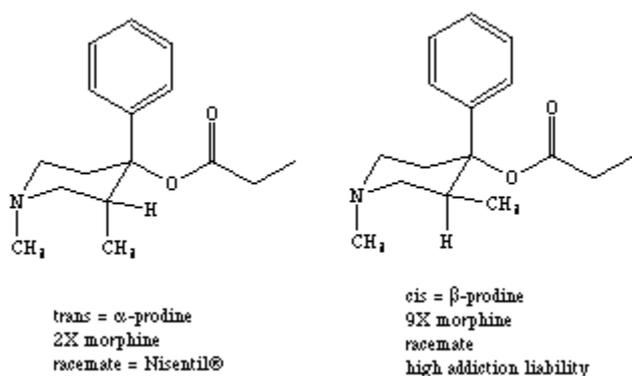


### Synthesis

To a stirred, cooled mixture of 298 parts of propionic acid and 175 parts of propionic anhydride, 85% phosphoric acid is added to a total of 150 parts. When heat is no longer liberated, there are slowly added 103 parts of N, N', N''-trimethyltrimethylenetriamine and 104 parts of  $\alpha$ -ethylstyrene. The mixture is stirred at 125° C for 18 hours, cooled, and poured into 3000 parts of water. The aqueous mixture is extracted with benzene [better toluene], thus removing unreacted olefinic material, and then made alkaline with caustic soda. Basic products separate. The alkaline mixture is extracted with benzene [better toluene]. The benzene solution is dried over potassium carbonate, and distilled. Fractionation under reduced pressure gave a fraction of 7 parts distilling at 30° - 80° C/1.5 mm, a fraction of 27 parts distilling at 80° - 120° C/1.5 mm, a fraction of 31 parts distilling at 120° - 160°C/1.5 mm, and 16 parts residue. The third fraction is redistilled at 120° - 135° C/1.5 mm. The product thus obtained contains 1,3-dimethyl-4-phenyl-4-propionoxypiperidine. It has a neutral equivalent of 259 (theory 261) and a refractive index at 25° C of 1.5387.

Note: It is possible to skip the phosphoric acid, which is only used as a catalyst. As the propionic anhydride is only used to bind the water in the phosphoric acid, it can then be substituted with propionic acid. Thereby, the use of propionic anhydride can be avoided at the price of a somewhat lower yield of 20 - 25%. Mix the acid and the styrene, slowly add the amine. Apply heat for 4 hours, then let stand for 2 days and continue as above.

### Pharmacology



From: Chemistry of Opioid Analgesics --PHY 422 - Neurology Pharmacotherapeutics

### Precursors

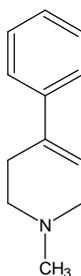
2-Phenyl-1-butene [2039-93-2], propionic acid, propionic anhydride and phosphoric acid are commercially available.

N, N', N''-Trimethyltrimethylenetriamine can easily be prepared:

76 parts by weight of aqueous 37% formaldehyde solution is slowly added to 84 parts by weight of aqueous 40% methylamine solution with stirring and cooling, the temperature of the reaction mixture being kept below 10°C. Solid caustic soda is then added in increments until two liquid phases form and separate. The upper layer is taken. The lower layer is extracted with benzene and the extracts are added to the upper layer. [You are well-advised to skip this step and accept a somewhat lower yield.] The resulting solution is dried over anhydrous potassium carbonate and distilled. At 65° - 75° C/35 mm, there is obtained a fraction of practically pure N, N', N''-trimethyltrimethylenetriamine or hexahydro-1,3,5-trimethyl-1,3,5-triazine in an amount of at least 36 parts by weight.

### MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)

is a neurotoxic compound which leads to irreversible parkinsonism. In certain syntheses of prodines this compound can be produced as a highly toxic contaminant. It seems unlikely, however, that MPTP is produced in the course of the synthesis outlined above.



**WARNING: It is illegal to perform the synthesis outlined above. Alphaprodine and betaprodine are controlled substances. Manufacturing these substances without appropriate license is a felony and leads to incarceration. Additionally, these compounds have the potential to be fatal if ingested. Be responsible! Know what you do!**