1, 2, 5-TRIMETHYL-4-AMINOPIPERIDINE AND 3, 6-DIMETHYL-4-PHENYL-2-AMINOPYRIDINE

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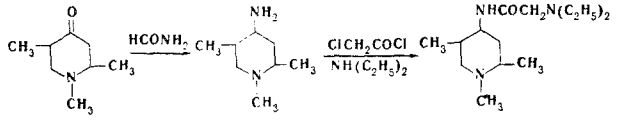
1, 2, 5-Trimethylpiperid-4-one is used to prepare 1, 2, 5-trimethyl-4-aminopiperidine, which is then converted to 1, 2, 5-trimethyl-4-(diethylaminoacetylamino)piperidine. Amination of 2, 5-dimethyl-4-phenylpyridine is effected, and 3, 6-dimethyl-4-phenyl-2-aminopyridine is thereby obtained.

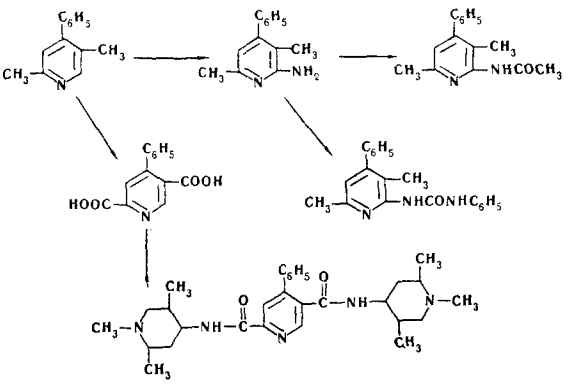
Continuing work on the synthesis and study of piperidine and pyridine derivatives, of possible pharmacological interest, attention was turned to synthesizing 1, 2, 5-trimethyl-4-aminopiperidine. The starting compound used to synthesize this aminopiperidine was 1, 2, 5-trimethylpiperid-4-one [1]. Reaction of piperidone with formamide gave a 30% yield of 1, 2, 5-trimethyl-4-aminopiperidine, this comparatively low yield due to the reaction proceeding to a considerable extent in the direction of giving high-boiling amino compounds, evidently mainly di(1,2,5-trimethylpiperidyl-4)amine.

Many aminoacyl derivatives of amines are local anesthetics with specific actions. The most interesting in this respect is xylocaine, 2-diethylaminoacetylamino-1, 3-dimethylbenzene, used in opthalmological work. To obtain similar piperidine compounds, 1, 2, 5-trimethyl-4-(diethylaminoacetylamino)piperidine has been synthesized. 1, 2, 5-Trimethyl-4-aminopiperidine was treated with chloroacetyl chloride, and the resultant 1, 2, 5-trimethyl-4-chloroacetylaminopiperidine then reacted with diethylamine.



Previously 2, 5-dimethyl-4-phenylpyridine [2] was synthesized starting from 1, 2, 5-trimethylpiperid-4-one [2]. Amination by the Chichibabin method converted this pyridine base to 3, 6-dimethyl-4-phenyl-2-aminopyridine. Acetylation of it gave 3, 6-dimethyl-4-phenyl-2-acetylaminopyridine, while treatment with phenyl isocyanate gave N-phenyl-N'-(3,6-dimethyl-4-phenylpyridyl-2)carbamate.

The paper mentioned above [2] also described a synthesis of 4-phenylpyridine-2, 5-dicarboxylic acid based on 2, 5-dimethyl-4-phenylpyridine. The dicarboxylic acid based on 2, 5-dimethyl-4-phenylpyridine. The dicarbonyl chloride from that acid gave, with 1, 2, 5-trimethyl-4-aminopiperidine, di(1, 2, 5-trimethylpiperidyl-4-amide)-4-phenylpyridine-2, 5-dicarboxylic acid.



EXPERIMENTAL

1, 2, 5-Trimethyl-4-aminopiperidine. 100 g (0.72 mole) 1, 2, 5-Trimethylpiperid-4-one was added, over a period of 1 hr, to formamide prepared from 160 g (1.67 mole) ammonium carbonate and 168 g (3.12 mole) 85% formic acid, and held at 170° C. After distilling off 17 ml water, the products were heated under reflux for 10 hr at 170°–180° C. 150 ml conc HCl was added, and the whole heated for 10 hr at 120°–130° C. The products were treated with KOH, extracted with ether, the solution dried and vacuum distilled. Yield 29.5 g 1, 2, 5-trimethyl-4-aminopiperidine, a mobile liquid bp 68°–82° C (4 mm); n_D^{20} 1.4746; d_4^{20} 0.8984. Found: MR_D 44.21, calculated for $C_8H_{18}N_2$: MR_D 44.39. Dipicrate mp 229°–231° C (ex EtOH). Found: N 18.80; 18.52%, calculated for $C_8H_{18}N_2 \cdot 2C_6H_3N_3O_7$: N 16.46%.

Also obtained is 30 g viscous liquid bp 134°–135° C (3 mm), n_D^{17} 1.5050, giving a picrate mp 70° C, evidently the hydrated form of the picrate of di(1, 2, 5-trimethylpiperidyl-4)amine. Found: N 16.00; 16.20%, calculated for $C_{16}H_{29}N_3 \cdot C_6H_3N_3O_7 \cdot H_2O$: N 16.46%.

1, 2, 5-Trimethyl-4-(diethylaminoacetylamino)piperidine. 23 g (0.2 mole) Chloracetyl chloride was added, with cooling, to 13 g (0.1 mole) 1, 2, 5-trimethyl-4-aminopiperidine in 50 ml dry toluene, and the mixture stirred for 3 hr at room temperature. The toluene and excess acid chloride were distilled off. 60 ml diethylamine was added to the residue cooled to 0° C. The mixture was stirred and refluxed for 10 hr, then the excess diethylamine distilled off. The residue was dissolved in water, and treated with Na_2CO_3. The products were extracted with ether, and the ether solution vacuum distilled to give 5.78 g starting 1, 2, 5-trimethyl-4-aminopiperidine and 7.6 g 1, 2, 5-trimethyl-4-(diethylaminoacetylamino)piperidine, bp 120°–126° C (2 mm); n_D^{19} 1.4790. Dipicrate mp 202°–203° C (ex EtOH). Found: N 17.74; 17.48%, calculated for $C_{14}H_{29}N_3O \cdot 2C_6H_3N_3O_7$: N 17.67%.

3, 6-Dimethyl-4-phenyl-2-aminopyridine. 30 g (0.16 mole) 2, 5-Dimethyl-4-phenylpyridine was added to freshly-prepared sodamide [250 ml liquid ammonia and 12 g (0.52 g-at) Na in 100 ml Me_2NH]. The mixture was heated for 6 hr at 180°–185° C. After cooling, 300 ml water and 100 ml 5% NaOH were added, then the mixture saturated with solid NaOH. A benzene extract of the reaction products gave 10 g

3, 6-dimethyl-4-phenyl-2-aminopyridine as pale yellow crystals, mp 118°–119° C (ex n-hexane). Found: N 13.88; 14.14%, calculated for $C_{13}H_{14}N_2$: N 14.13%.

2 ml Ac_2O was added to a mixture of 0.5 g (2.5 mM) 3, 6-dimethyl-4-phenyl-2-aminopyridine and 8 ml 20% NaOH solution. The oil that separated was extracted with benzene. Distilling off the benzene and recrystallizing gave 0.6 g colorless crystals of 3, 6-dimethyl-4-phenyl-2-acetylaminopyridine, mp 98°–98.5° C (ex benzene). Found: N 11.15; 11.29%, calculated for $C_{15}H_{16}N_2O$: N 11.67%.

A mixture of 0.2 g (1 mM) 2, 6-dimethyl-4-phenyl-2-aminopyridine and 3 ml phenyl isocyanate was heated for 15 min. The product was 0.1 g of N-phenyl-N'-(3, 6-dimethyl-4-phenylpyridyl-2)carbamate, mp 193°–194° C (ex CCl_4). Found: N 12.96; 12.81%, calculated for $C_{20}H_{19}N_3O$.

Di(1, 2, 5-trimethylpiperidyl-4-amide) of 4-phenylpyridine-2, 5-dicarboxylic acid. 10 g (0.07 mole) 1, 2, 5-Trimethyl-4-aminopiperidine was added at room temperature to 4-phenylpyridine-2, 5-dicarbonyl chloride, prepared from 5 g (0.02 mole) of the dicarboxylic acid and 30 ml thionyl chloride in 20 ml toluene. The mixture was refluxed for 8 hr, the toluene distilled off, the residue treated with Na_2CO_3 solution, and extracted with $CHCl_3$. The extract gave 3.5 g di(1, 2, 5-trimethylpiperidyl-4-amide) of 4-phenylpyridine-2, 5-dicarboxylic acid, mp 230° C (ex acetone-EtOH). Found: N 14.54%, calculated for $C_{29}H_{39}N_5O_2$: N 14.31%.

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