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SYNTHESIS OF LEPIDINE AND ITS DERIVATIVES FROM AROMATIC AMINES AND QUATERNARY SALTS OF MANNICH BASES

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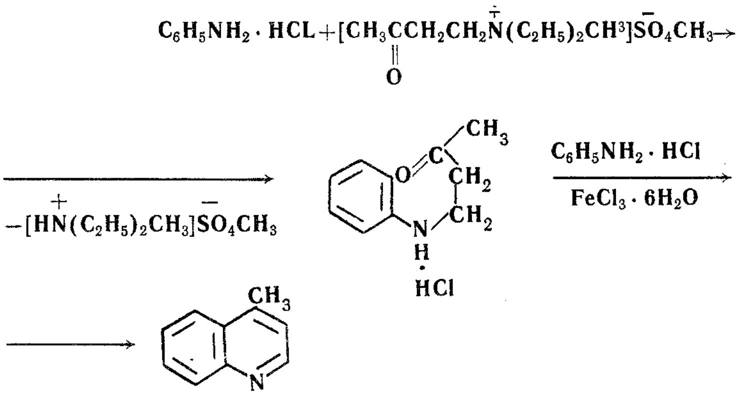
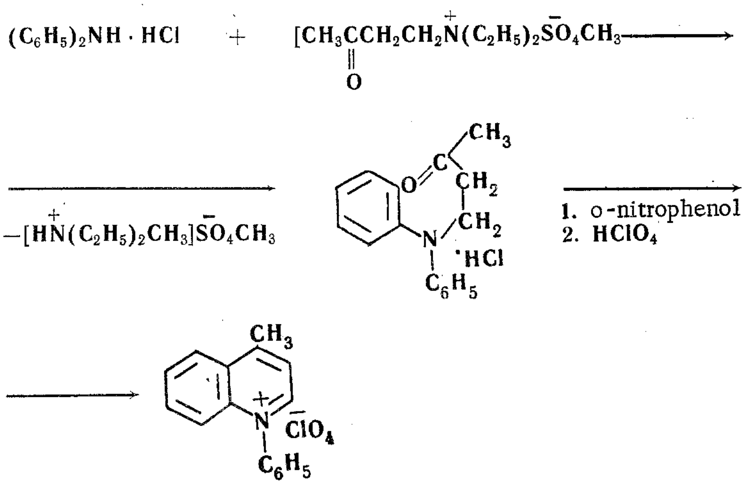
A quaternary salt of 4-(diethylamino) butan-2-one, methyldiethyl-3-ketobutylammonium methyl sulfate, is used as an alkylating agent to synthesize lepidine and 1-phenyllepidine salts. The method gives good yields, under mild conditions, of lepidine and 1-phenyllepidine perchlorate. An intermediate product is isolated, and a reaction mechanism suggested.

A preceding paper showed that lepidine and its derivatives are obtained in good yield from aromatic amines and salts of Mannich bases, e.g., from 4-(diethylamino) butan-2-one hydrochloride [1, 2]. However, this synthesis takes place at 135° C, and necessitates the use of a high-boiling solvent. The present paper offers a modification of that synthesis. The alkylating agent used is a quaternary salt of 4-(diethylamino) butan-2-one, methyldiethyl-3-ketobutylammonium methyl sulfate.



Here reaction proceeds in ethanol. A 65% yield of lepidine is obtained by heating aniline hydrochloride with methyldiethyl-3-ketobutylammonium methyl sulfate in the presence of ferric chloride hexahydrate and zinc chloride. Use of nitrobenzene or o-nitrophenol as the oxidizing agent reduces the yield of lepidine to, respectively, 40 and 45%.

Use of diphenylamine in the reaction gives 1-phenyllepidine perchlorate in 28% yield. Other methods of preparing 1-phenyllepidine give considerably lower yields [3-7]. The best yield of 1-phenyllepidine perchlorate is obtained by using o-nitrophenol as the oxidizing agent (28% instead of the 23% obtained using nitrobenzene).



It should be mentioned that use of zinc chloride cuts the yield of 1-phenyllepidine perchlorate to 16%. Zinc chloride raises the yield in the synthesis of quinoline salts from unsaturated carbonyl compounds [4, 5, 8].

In the synthesis of lepidine, the intermediate compound is β-anilinoethylmethylketone, formed from aniline and the quaternary salt of 4-(diethylamino) butan-2-one. β-Anilinoethylmethylketone was obtained in good yield by heating the starting materials with water, and converted in good yield to lepidine. The reaction involving secondary amines takes place similarly. A paper [9] reports preparation of β-diphenylaminopropiophenone from diphenylamine and β-dimethylaminopropiophenone. Evidently alkylation of aromatic amines by quaternary salts of Mannich bases proceeds via a stage of decomposition of the Mannich base to give unsaturated ketone and tertiary amine.

Experimental

Methyldiethyl-3-ketobutylammonium methylsulfate. 12.6 g (0.1 mole) Me_2SO_4 was added dropwise, with vigorous stirring and strong cooling, to 14.3 g (0.1 mole) 4-(diethylamino) butan-2-one. The viscous oil which the quaternary salt formed, was used for the further work.

Triethyl-3-ketobutylammonium ethylsulfate. 14.3 g (0.01 mole) 4-(diethylamino) butan-2-one was mixed with 15.4 g (0.1 mole) Et_2SO_4. Reaction, which was accompanied by slight heating, was complete in a few hours. The mixture was heated to 50-60° C to bring about rapid reaction; in that case there was marked heat evolution, and the mixture was cooled so as to hold the temperature at 60° C.

Lepidine. A mixture of 16.3 g (0.125 mole) aniline hydrochloride, 54 g (0.2 mole) $FeCl_3 \cdot 6H_2O$, 2 g $ZnCl_2$, and 100 ml ethanol was refluxed on a water bath, and a solution of 26.9 g (0.1 mole) methyldiethyl-3-ketobutylammonium methylsulfate in 20 ml ethanol added dropwise over 60-90 min, after which heating was continued for 6 hr more. Most of the solvent was then distilled off under reduced pressure, the residue made alkaline with 20% NaOH solution, and the lepidine distilled off with steam superheated to 130° C. The lepidine was extracted from the distillate with ether. To separate the aniline, [10], the ether solution was dried over anhydrous Na_2SO_4, 15 g powdered phthalic anhydride added, and the mixture carefully stirred for an hour. The products were then made alkaline with 5-7% NaOH solution. The ether layer was separated off, washed with water, and dried. The lepidine was distilled, taking a cut bp 124—125° C (15–16 mm), n_D^{20} 1.6190. Yield of lepidine 9.3 g (65%). Picrate mp 214° C. Undepressed mixed mp with authentic lepidine picrate. When the synthesis was run in PrOH, the lepidine yield was 55%.

β-Anilinoethylmethylketone. 21 g (0.225 mole) aniline was dissolved in 500 ml boiling water, and 40.4 g (0.15 mole) methyldiethyl-3-ketobutylammonium methylsulfate added. The mixture was refluxed for 1 hr, cooled, and the oil which separated extracted with ether, dried over Na_2SO_4, and, after evaporating off the ether, distilled, yield 14.0 g (57%), bp 145–150° C (5 mm). The literature gives 135–140° (8 mm)[9]; 140–142° (6 mm) [11].

Cyclizing β-anilinoethylmethylketone. A mixture of 12.9 g (0.1 mole) aniline hydrochloride, 54 g (0.2 mole) $FeCl_3 \cdot 6H_2O$, 2 g $ZnCl_2$, and 100 ml EtOh was refluxed, and a solution of 16.3 g (0.1 mole) β-anilinoethylmethylketone in 20 ml EtOH added dropwise. Refluxing was for 3 hr, after which the lepidine was isolated as described above, yield 57%.

1-Phenyllepidine perchlorate. 16.9 g (0.1 mole) diphenylamine was dissolved in 100 ml PrOH and HCl gas passed in until there was a gain in weight of 10–11 g. 26 g o-nitrophenol was added to the mixture, which was then heated to boiling, under reflux, and 33.8 g (0.125 mole) methyldiethyl-3-ketobutylammonium methylsulfate dissolved in 25 ml PrOH added dropwise. After this, heating was continued for 4 hr more. Next most of the solvent was distilled off under reduced pressure, and the o-nitrophenol removed by steam distillation. The aqueous solution of 1-phenyllepidine hydrochloride was separated from the tar which clung to the flask walls, and boiled with 5–10 g active charcoal. Then a dilute solution of $HClO_4$ was added to precipitate 1-phenyllepidine perchlorate, yield 9.0 g, 28% , mp 174° C. Found: Cl 11.06, 11.07%. Calculated for $C_{16}H_{14}ClNO_4$: Cl 11.09%.

Similar results were obtained when triethyl-3-ketobutylammonium ethylfulfate was used to synthesize lepidine and 1-phenyllepidine perchlorate.

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