[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

THE SYNTHESIS OF N-METHYL-4-PIPERIDYL TROPYLATE

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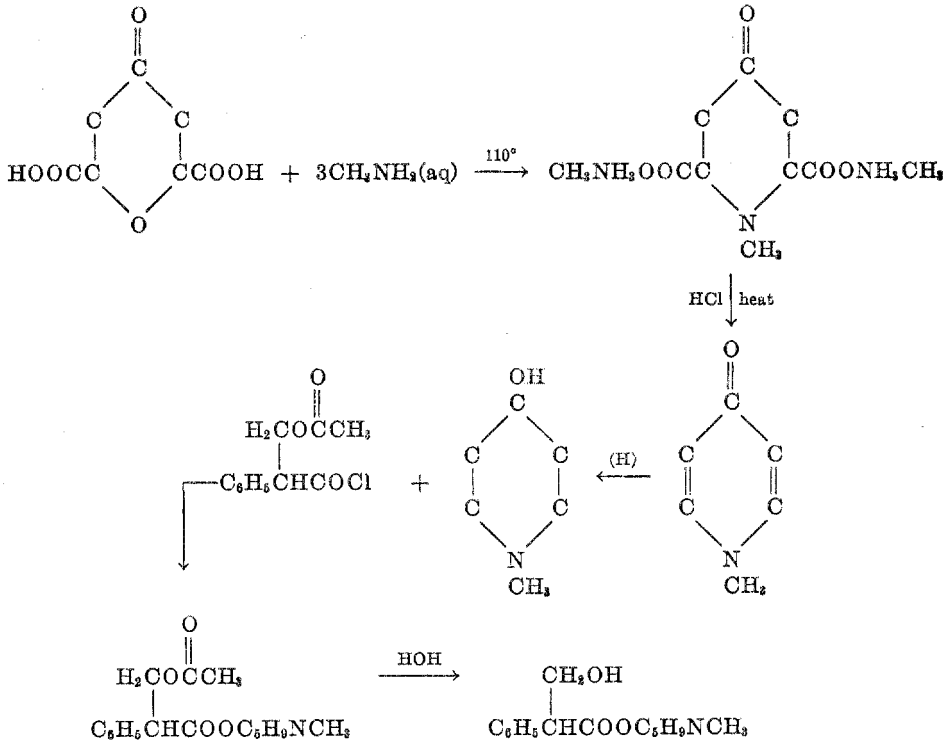
Received June 2, 1952

Several compounds having anesthetic properties have been prepared from N-alkyl-4-hydroxypiperidines (1–3). Still others (4) are esters of tropic acid. This paper describes the synthesis of the tropic acid ester of N-methyl-4-hydroxypiperidine.

The synthesis of the alcoholic portion is essentially that of Willstätter (5), simplified in part by Riegel and Zwilgmeyer (6). The reactions involved are as follows:



EXPERIMENTAL

Chelidonic acid. To 500 g. of absolute ethanol in a flask fitted with a reflux condenser, 46 g. (2 g.-atoms) of sodium was added in small portions. After completion of the reaction, half of this mixture was added, with stirring, to a mixture of 58 g. (1 mole) of acetone mixed with 150 g. (1.03 moles) of ethyl oxalate. When the solution became turbid, 160 g. (1.1 moles) of ethyl oxalate and the remaining sodium ethoxide solution were added. Chelidonic ester precipitated after about ten minutes. The alcohol was removed by distillation, and a mixture of 300 ml. of concentrated hydrochloric acid and 800 g. of cracked ice was added and mixed for two hours to ensure complete neutralization of the sodium ethoxide. The es-

ter was then filtered, washed with cold water, and hydrolyzed by heating on a steam-bath with 300 ml. of concentrated hydrochloric acid for 20 hours. The acid was filtered, washed with cold water, and dried at 160° to remove water of crystallization. Yield, 72%.

N-Methylchelidamic acid. To 87 g. (0.47 mole) of chelidonic acid was added 225 ml. of 25% methylamine solution. The mixture was then placed in a Carius tube and heated at 110° for 24 hours. On removal, the mixture was acidified with hydrochloric acid and the N-methylchelidamic acid was filtered, washed, and carefully dried at 120°. Yield, 89%.

N-Methyl-4-pyridone. To promote decarboxylation, 63.5 g. (0.32 mole) of N-methylchelidamic acid was slowly heated, and then distilled at 12 mm. Yield, 86%.

N-Methyl-4-hydroxypiperidine. Into a 2-liter flask containing 650 g. (14 moles) of ethanol and 42 g. (0.38 moles) of N-methyl-4-pyridone, 59 g. (2.56 moles) of sodium was introduced slowly with stirring. After reaction was complete, the mixture was acidified with alcoholic hydrogen chloride to precipitate sodium chloride. An excess of ammonium hydroxide was then added and the contents were allowed to stand for 12 hours. After filtering, the solution was vacuum-distilled, the pure product boiling at 83° under 8 mm. Yield, 46.5%.

Acetyltropyl chloride. To a 25-ml. Erlenmeyer flask containing 5.2 g. (0.064 mole) of acetyl chloride was added 3 g. (0.018 mole) of tropic acid. The solution was placed on a water-bath, stirred for 15 minutes, and placed under suction overnight. The acetyltropic acid formed was then heated for two hours with 15 ml. of thionyl chloride, and the liquid was evaporated until it became quite viscous. A small amount of benzene was added and sucked off to eliminate any traces of thionyl chloride. The acetyltropyl chloride was used immediately.

N-Methyl-4-piperidyl tropylate. To the acetyltropyl chloride was added 1.31 g. (0.009 mole) of N-methyl-4-hydroxypiperidine hydrochloride, previously prepared by treating the basic alcohol with alcoholic hydrogen chloride. The slurry was heated on a steam-bath for two hours. When a sample treated with water showed only slight turbidity the reaction was considered complete.

The acetyl group was hydrolyzed by heating the viscous oil for 15 minutes with 15 ml. of water. Upon the addition of a cold sodium hydroxide solution the desired product separated as a heavy oil. The ester was washed thoroughly with cold water and dissolved in acetone and benzene in an attempt to crystallize the product. Crystallization was accomplished by scratching with a glass rod underneath a layer of water. Yield, 50–55%.

Anal. Calc'd for $C_{15}H_{21}NO_3$: N, 5.32; Mol. wt., 263.

Found: N, 5.25; Mol. wt., 264.

Nitrogen was determined by the micro Kjeldahl method.

Molecular weight was determined by the cryoscopic method, using glacial acetic acid as solvent.

SUMMARY

N-Methyl-4-piperidyl tropylate has been synthesized.

The compound is similar to atropine in structure, lacking the 2,6-ethylene bridge.

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