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2,765,315

PREPARATION OF ESTERS

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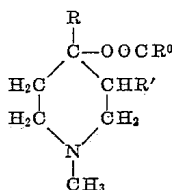
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This invention deals with a method for preparing esters of lower monocarboxylic acids and 1-methyl-4-piperidinols having also a hydrocarbon substituent in the 4-position.

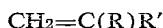
Synthesis of various 1-alkyl-4-aryl-4-acyloxypiperidines has been accomplished through reaction of lithium aryls or arylmagnesium halides with 1-alkyl-4-piperidones followed by acylation. These esters have been shown to act as analgesics. The methods of preparing such compounds have been rather cumbersome and tedious.

We have discovered a more direct and convenient method for making esters of the structure

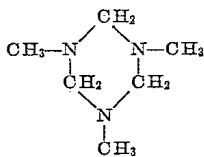


wherein R is a phenyl group or a methyl group, R⁰ is an alkyl group, preferably of one to two carbon atoms, and R' is hydrogen or methyl.

Our process comprises reacting an α -methylstyrene, an α -ethylstyrene, isobutylene, or 2-methyl-1-butene, which may be represented by the formula



where R is phenyl or methyl and R' is methyl or ethyl, with N,N',N''-trimethylhexahydro-1,3,5-triazine of the structure



and a monocarboxylic acid of the formula R⁰COOH, where R⁰ is an alkyl group, particularly an alkyl group of not over two carbon atoms. These three reactants are mixed and the mixture is heated between 80° and 125° C. The reaction proceeds more readily when phosphoric acid is added to the reaction mixture. We have successfully operated with no phosphoric acid up to over a mole of phosphoric acid per mole of olefin, the common 85% orthophosphoric acid being used for this purpose. Conveniently acid anhydride may be added to dispose of water in the acid. We have also found various complex or polyphosphoric acids helpful.

There is theoretically required at least one mole of carboxylic acid per mole of olefin, but an excess seems generally desirable. Excess acid serves as a solvent.

About an equivalent of the N,N',N''-trimethyltrimethylenetriamine should be used per mole of olefin. The proportion used need not, however, be exact.

As a monocarboxylic acid there is used acetic or propionic acid by choice, although longer chained acids can be reacted. It is helpful to use along with the acid

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some of its anhydride or the anhydride may be used as the equivalent of the acid.

The above triamine is prepared, as has been shown, from methylamine and formaldehyde. Theoretically at least, other primary amines could be used in the place of methylamine, such as ethylamine, butylamine, allylamine, benzylamine, or cyclohexylamine. The formaldimine which forms tends to trimerize. The reaction is completed by added caustic soda until the mixture separates into two phases, the upper layer being the desired product.

In a typical preparation of this reactant, 76 parts by weight of aqueous 37% formaldehyde solution is slowly added to 83 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. 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.

Typical preparations according to this invention are presented in the following illustrative examples wherein parts are by weight.

Example 1

There are mixed 250 parts of glacial acetic acid and 190 parts of α -methylstyrene. Thereto is slowly added N,N',N''-trimethylhexahydro-1,3,5-triazine to a total of 36 parts. The mixture is stirred and heated at 95° C. for four hours and left standing for two days. The reaction mixture is then poured into about 700 parts of water. This mixture is extracted with benzene. It is now made basic by adding aqueous caustic soda solution. The basic material which separates is taken up in benzene and the water layer is extracted with benzene. The combined benzene solutions are dried over potassium carbonate and distilled. Between 82° and 122° C./2 mm. a forerun of 9 parts is taken off. At 122°–132° C./2 mm. a fraction of 23 parts is distilled off. This is quite pure 1-methyl-4-phenyl-4-acetoxypiperidine. When this fraction is stirred and cooled, it crystallizes. Upon recrystallization from heptane, the product melts at 62°–64° C. It contains by analyses 72.0% of carbon, 8.34% of hydrogen, and 5.97% of nitrogen. It gives a neutral equivalent of 230. Theoretical values are carbon 72.07%, hydrogen 8.21%, and nitrogen 6.00%, with a theoretical neutral equivalent of 233.

Example 2

There are mixed 210 parts of glacial acetic acid, 60 parts of acetic anhydride, and 58 parts of orthophosphoric acid with cooling. There are added to this mixture 65 parts of 1,3,5-trimethylhexahydro-1,3,5-triazine and 59 parts of α -methylstyrene. The resulting reaction mixture is stirred and heated at 115° C. for four hours, allowed to stand for two days, and poured into 500 parts of water. The aqueous mixture is extracted with benzene and then made alkaline by the addition of aqueous caustic soda solution. A basic organic product separates and is taken up in benzene. The benzene layer is taken off, dried over anhydrous potassium carbonate, and distilled. A fraction is taken off at 70°–100° C./0.85 mm. and then another fraction of 35 parts is obtained at 100°–120° C./0.85 mm. This corresponds in composition to 1-methyl-4-phenyl-4-acetoxypiperidine. A residue of 19 parts remains. The 1-methyl-4-phenyl-4-acetoxypiperidine crystallizes when stirred and cooled. The crystals melt at 61°–62° C. after recrystallization from heptane.

