Patented May 12, 1953 2,638,478

UNITED STATES PATENT OFFICE

2,638,478

PHOSPHORUS-CONTAINING DERIVATIVES OF M-AMINO-PHENOLS

Alexander Lang Morrison and Frank Ratcliffe Atherton, Welwyn Garden City, England, assignors to Hoffmann-La Roche Inc., Nutley, N. J., a corporation of New Jersey

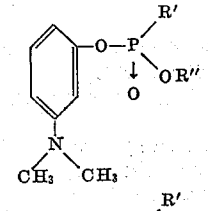
No Drawing. Application May 3, 1950, Serial No. 159,858. In Great Britain May 4, 1949

6 Claims. (Cl. 260—461)

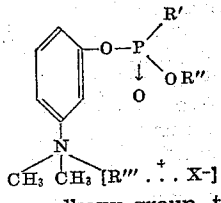
1

This invention relates to new phosphorus-containing derivatives of m-dimethylaminophenol, more particularly dialkyl phosphates and alkyl alkyl (or aryl) phosphonates of m-dimethylaminophenol and quaternary salts thereof.

The new compounds of the present invention may be represented by the following general formulae:



I.



II.

wherein R′ is an alkoxy group, the alkyl group of which contains not more than eight carbon atoms (including isoalkyl and cyclohexyl groups) or an alkyl group which contains not more than eight carbon atoms (including isoalkyl and cyclohexyl groups) or an aryl group, R″ is an alkyl group containing not more than eight carbon atoms (including isoalkyl and cyclohexyl groups), R‴ is an alkyl or alkenyl group containing not more than four carbon atoms or an aralkyl group, e. g. a benzyl group, and X is a monovalent anion. Preferred monovalent anions are the chloride, bromide, iodide and methyl sulphate anions.

The present specification also includes a process for the manufacture of dialkyl phosphates and alkyl alkyl (or aryl) phosphonates of m-dimethylaminophenol of the general Formula I wherein m-dimethylaminophenol in the form of an alkali metal derivative is reacted with a dialkyl halogenophosphonate or an alkyl alkyl (or aryl) halogenophosphonite. These compounds can be readily converted into their quaternary salts of general Formula II in a manner which is known per se.

The quaternary compounds of the present invention have an anticholinesterase activity which renders them useful as pharmaceuticals.

The dialkyl halogenophosphonate or the alkyl alkyl (or aryl) halogenophosphonite used as the reagent for the introduction of the phosphorus-containing radical into the m-aminophenol is

2

preferably the chloro-compound. Examples of such preferred reagents are:

Dimethyl chlorophosphonate
Diethyl chlorophosphonate
Di-(n or iso)-propyl chlorophosphonate
Methyl methylchlorophosphonite
Ethyl ethylchlorophosphonite
Ethyl phenylchlorophosphonite

The following examples illustrate how the process of the invention may be carried into effect.

EXAMPLE 1

m-Dimethylaminophenyl-diethyl phosphate

An ethanolic solution of the sodium salt of m-dimethylaminophenol is prepared by adding m-dimethylaminophenol (7.54 g., 0.055 M) to a solution of sodium ethoxide, made by dissolving metallic sodium (1.4 g., 0.061 M) in absolute ethanol (80 ml.), maintained in a nitrogen atmosphere. Diethyl chlorophosphonate (10.51 g., 0.061 M) is added in one portion and the mixture is refluxed with stirring for two hours. After cooling, the precipitated sodium chloride is filtered and washed with alcohol and the filtrate is evaporated under reduced pressure. The residual oil is dissolved in carbon tetrachloride (50 ml.) and the solution is washed with sodium hydroxide solution (3 x 40 ml. normal solution) and water (3 x 40 ml.). After drying over potassium carbonate, the drying agent is filtered off and the filtrate evaporated under reduced pressure in a water pump. Distilled under mercury diffusion pump vacuum, the product boils at 116°–120° C./3 x 10^{-3} mm. The yield of m-dimethyl aminophenyl-diethyl phosphate is 10.9 g. (=73%), n_D^{22}=1.5112.

EXAMPLE 2

m-Dimethylaminophenyl-di-isopropyl phosphate

m-Dimethylaminophenyl - di - isopropyl phosphate is prepared in a manner similar to that of Example 1 from m-dimethylaminophenol (8.22 g., 0.06 M), sodium (1.65 g., 0.072 M), isopropyl alcohol (80 ml.) and di-isopropyl chlorophosphonate (14.37 g., 0.072 M). It boils at 110°–114° C./1 x 10^{-4} mm. The yield of m-dimethylaminophenyl - di - isopropyl phosphate is 12.25 g. (=68%) n_D^{22}=1.5102.

EXAMPLE 3

m-Dimethylaminophenyl-dimethyl phosphate

m-Dimethylaminophenol (6.85 g.) is dissolved in ethanolic sodium ethoxide (1.25 g. Na; 60 ml.

ethanol) in a nitrogen atmosphere and dimethylchlorophosphonate (8 g.) is added dropwise over about 15 minutes. There is an immediate precipitate of sodium chloride and the mixture is heated under reflux for 15 hours. The sodium chloride is filtered off and the alcohol evaporated from the filtrate in vacuo. The residue is dissolved in carbon tetrachloride (ca. 50 ml.) and the solution extracted three times with N/2 sodium hydroxide and three times with water. The solution is dried over anhydrous sodium sulphate and the carbon tetrachloride evaporated in vacuo. Distillation of the residual brown oil gives the required product, i. e. m-dimethylaminophenyl-dimethyl phosphate as a colorless oil, in 50% yield; B. P. 120°–123° C. at 0.05 mm.

EXAMPLE 4

m - Dimethylaminophenyl - dimethylphosphate - methyl-methyl sulphate

A solution of m-dimethylaminophenyl-dimethyl phosphate (1.8 g.) in dry benzene (60 ml.) and dimethyl sulphate (1 ml.) is allowed to stand for 30 hours at 15° C. during which time the methyl-methyl sulphate crystallises out. Ether is added and the crystals (M. P. 82°–84° C.) are collected. The yield amounts to 66%. Recrystallisation from alcohol-ethyl acetate-ether gives colorless plates of m-dimethylaminophenyl-dimethylphosphate-methyl-methyl sulphate; M. P. 84°–86° C.

EXAMPLE 5

m - Dimethylaminophenyl - diethylphosphate - methyl-methyl sulphate

A solution of m-dimethylaminophenyl-diethyl phosphate (6 g.) in dry benzene (15 ml.) and dimethyl sulphate (3 ml.) is allowed to stand for 43 hours. The procedure is as in Example 4. The yield of m-dimethylaminophenyl-diethylphosphate-methyl-methyl sulphate is 72%; M. P. 101°–103° C.

EXAMPLE 6

m-Dimethylaminophenyl-di-isopropyl phosphate methyl-methyl sulphate

A solution of m-dimethylaminophenyl-di-isopropyl phosphate (3 g.) in dry benzene (8 ml.) and dimethyl sulphate (1.4 ml.) is allowed to stand for 2 days. An oil separates which is induced to crystallise from alcohol-ethyl acetate-ether. The yield is 55%; M. P. 68°–72° C. (deliquescent). Repeated recrystallisations give small colorless needles of m-dimethylaminophenyl-di-isopropyl phosphate methyl-methyl sulphate, M. P. 82°–84° C.

EXAMPLE 7

m-Dimethylaminophenyl-di-sec-butyl phosphate

m-Dimethylaminophenol (6.9 g.) is dissolved in ethanolic sodium ethoxide (1.4 g. Na; 70 ml. ethanol) in a nitrogen atmosphere and di-sec-butyl-chlorophosphonate (13.7 g.) is added dropwise over 30 minutes. The procedure is as in Example 4. The yield of m-dimethylaminophenyl-di-sec-butyl phosphate is 62.5%; B. P. 119°–124° C. at 2.3×10^{-5} to 2.8×10^{-4} mm.

EXAMPLE 8

m - Dimethylaminophenyl - di - sec - butyl phosphate-methyl-methyl sulphate

A solution of m-dimethylaminophenyl di-sec-butyl phosphate (1.65 g.) in dry benzene (4 ml.) and dimethyl sulphate (0.7 ml.) is allowed to stand for 2 days. The preparation proceeds as in Example 4. Hygroscopic colorless plates of m-dimethylaminophenyl-di-sec-butyl phosphate-methyl-methyl sulphate are obtained, M. P. 90°–92° C.

We claim:

1. A compound selected from the group consisting of m-dimethylaminophenyl-di-lower alkyl phosphates and the quaternary ammonium salts thereof.
2. m-Dimethylaminophenyl-diethyl phosphate.
3. m - Dimethylaminophenyl - dimethylphosphate-methyl-methyl sulphate.
4. m-Dimethylaminophenyl-diethylphosphate-methyl-methyl-sulphate.
5. m-Dimethylaminophenyl-di-isopropyl phosphate methyl-methyl sulphate.
6. m-Dimethylaminophenyl-di-sec-butyl phosphate-methyl-methyl sulphate.

ALEXANDER LANG MORRISON.
FRANK RATCLIFFE ATHERTON.

References Cited in the file of this patent

FOREIGN PATENTS

Number	Country	Date
257,649	Switzerland	May 2, 1949