

UNITED STATES PATENT OFFICE

2,541,717

PTERINE IMINES

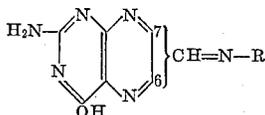
Harold G. Petering, Kalamazoo, Mich., assignor
to The Upjohn Company, Kalamazoo, Mich., a
corporation of Michigan

No Drawing. Application October 18, 1948,
Serial No. 55,235

9 Claims. (Cl. 260—240)

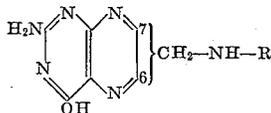
1

This invention relates to the condensation of pterine [pyrimido-(4,5b)-pyrazine] aldehydes with primary amines and the 2-amino-4-hydroxy-6-(and 7-)methylenepterine imines resulting therefrom. Among the preferred imines of the present invention are those represented by the formula:



wherein R is an alkyl, aryl, or a para-monosubstituted aryl radical. Among the para-monosubstituted aryl groups contemplated by this invention are those which would result from the removal of one hydrogen atom from the para position in benzoic acid, esters of benzoic acid, benzamide, benzoylglutamic acid and esters and amides of benzoylglutamic acid i. e. radicals from the group consisting of the para-carboxyphenyl and the para-(N-(1,3-dicarboxypropyl) carbamido)-phenyl radicals, their esters and amides.

The compounds of this invention are useful intermediates in the synthesis of other pterine compounds. For example, by reduction, compounds may be obtained represented by the formula:



R having the values above-given. Among such compounds are pteric acid, pteroyl glutamic acid, rhizopterines and related compounds. The products of this invention are yellow to orange crystalline solids, soluble without decomposition in cold aqueous alkalies and acids, sparingly soluble in water and relatively insoluble in most common organic solvents. They char and decompose without definite melting above 300 degrees centigrade. They are characterized by their ultraviolet absorption spectra and in particular by the ratios of their extinction coefficients at the absorption maxima.

The 2-amino-4-hydroxy-6- (and 7-)formylpterines from which the imines of this invention are obtained are described and their preparation by oxidizing 2-amino-4-hydroxy-6- (and 7-) polyhydroxyalkylpterines is described and claimed in copending application Serial No. 55,234, filed October 18, 1948, by Harold G. Petering et al. The 2-amino-4-hydroxy-6- (and 7-) polyhy-

2

droxyalkylpterines from which the aldehydes are obtained and their preparation are described and claimed in the copending application Serial 32,983, filed June 14, 1948. According to the methods of the copending applications the 2-amino-4-hydroxy-6- (and 7-) polyhydroxyalkylpterines can be prepared by reacting the osone of a monosaccharide having at least four carbon atoms with 2,4,5-triamino-6-hydroxypyrimidine or an acid addition salt thereof, hereinafter referred to as a 2,4,5-triamino-6-hydroxypyrimidine compound, in aqueous solution at a pH between about 4.5 and about 9.0. The above reaction is accelerated by moderate heating, as on a steam bath. The desired product can be precipitated from the reaction mixture by acidification to a pH of 4.5 or less. The crude product thus precipitated can be separated, as by filtration, and may then be purified by dissolving in dilute alkali, decolorizing with adsorbent charcoal, and, recovered by acidification and filtration.

The 2-amino-4-hydroxy-6-polyhydroxyalkyl-, and 2-amino-4-hydroxy-7-polyhydroxyalkylpterines thus obtained can be oxidized to 2-amino-4-hydroxy-6-formyl- and 2-amino-4-hydroxy-7-formylpterines respectively as by means of lead tetraacetate. In order to carry out this invention an excess of purified lead tetraacetate, dissolved in warm glacial acetic acid or a mixture of glacial acetic acid and acetic anhydride, is mixed with a solution of the polyhydroxyalkylpterine in water. The reaction is rapid and exothermic. While the starting polyhydroxyalkylpterines may be dissolved in hot water as above, in which they are soluble to the amount of about one-half per cent at 100 degrees centigrade, it is preferred that small amounts of alkali, such as an alkali metal hydroxide, carbonates and bicarbonates and ammonium hydroxide, be used to effect solution. Alternatively the aqueous solution can be acidified to about pH 3 prior to the addition of the lead tetraacetate solution. However, the use of small quantities of alkali is a preferred procedure as the volume of solution required is sufficiently reduced to be of practical importance. An alkaline solution can be used to dissolve the starting polyhydroxyalkylpterine since the large excess of acid added along with the lead tetraacetate assures that the resulting aldehyde will not be destroyed by the added alkali.

The exothermic nature of the reaction causes the temperature to rise to about 80 to 90 degrees centigrade, the final temperature being dependent upon the volume of the solutions. After mix-