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UNITED STATES PATENT OFFICE

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N-DIALKYLAMINOALKYL DERIVATIVES OF α,β-DIARYLALKANOAMIDES AND THEIR SALTS

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7 Claims. (Cl. 260—558)

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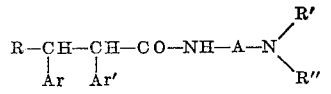
The present invention is concerned with a new type of amide of α,β-diarylalkanoic acid and salts thereof. In particular, it relates to N-dialkylaminoalkyl derivatives of α,β-diarylalkanoamides of the structural formula



and salts thereof, wherein Ar and Ar' are lower aryl radicals, A is a saturated, bivalent, lower aliphatic hydrocarbon radical containing at least two carbon atoms, R is a lower alkyl radical, and the radical NR'R'' is a member of the class consisting of dialkylamino radicals and saturated nitrogen-containing heterocyclic radicals attached to the alkylene radical A through a nitrogen in the heterocycle.

In the foregoing structural formula Ar and Ar' may represent such lower aromatic hydrocarbon radicals as phenyl, tolyl, xylyl, naphthyl, methylnaphthyl, ethylnaphthyl, dimethylnaphthyl and the like. The radical A represents a bivalent, saturated, aliphatic hydrocarbon radical of from two to eight carbon atoms; this radical is derived from a straight-chain or branched-chain aliphatic hydrocarbon and includes radicals such as ethylene, propylene, butylene, amylene, or polymethylene radicals such as trimethylene, tetramethylene, pentamethylene, and hexamethylene. The radical R may represent such lower alkyl groups as methyl, ethyl, propyl, butyl, amyl, hexyl, cyclopentyl and cyclohexl, wherein the propyl, butyl, amyl and hexyl groups may be either of the straight-chain or branch-chain type. The radicals R' and R'' may be of the same type as radical R. In addition the radical NR'R'' can also be a saturated nitrogen-containing heteromonocyclic group attached to the radical A through a nitrogen in the heteromonocycle; examples of such heteromonocycles are: N-piperidino, N-lupetidino, N-pyrrolidino, N-morpholino, N-thiamorpholino, N'-alkyl-N-piperazino and like radicals.

The organic bases of the foregoing type form salts with a variety of inorganic and strong organic acids including sulfuric, phosphoric, hydrochloric, hydrobromic, sulfamic, citric, ascorbic and related acids. They also form quaternary ammonium salts with a variety of organic esters of sulfuric, hydrohalic and aromatic sulfonic acids. Among such esters are methyl chloride and bromide, ethyl chloride, propyl chloride, butyl chloride, isobutyl chloride, benzyl chloride and bromide, phenethyl bromide, naph-

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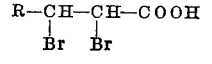
thylmethyl chloride, dimethyl sulfate, diethyl sulfate, methyl benzene sulfonate, ethyl toluene sulfonate, ethylene chlorohydrin, propylene chlorohydrin, allyl bromide, methallyl bromide and crotyl bromide.

The object of this invention is to provide novel amides of α,β-diarylalkanoic acids. Certain of these amides are valuable intermediates in organic synthesis. Others have been found to possess a number of useful pharmacodynamic properties. Thus the amides have a pronounced effect on the cardiovascular function and a potent diuretic effect on renal excretory function.

My invention is disclosed in further detail in the following experimental part, which is set forth for the purpose of illustrating the invention and is in no way to be construed as limiting the invention in spirit or in scope. It will be apparent to those skilled in the art that many conventional modifications in methods, conditions, and materials can be adopted without departing therefrom. In each case temperatures are given uncorrected in degrees centigrade (° C.) and quantities in parts by weight.

α,β-Diarylalkanoic acids

The literature provides a number of useful procedures for the preparation of these acids. Thus saponification of the nitrile was employed by Plentl and Bogert (J. Am. Chem. Soc., vol. 63, pages 989 et seq.; 1941) for the preparation of α,β-diphenylbutyric acid and by Kohler (Am. Chem. J., vol. 35, page 91; 1906) for the preparation of α,β-diphenylvaleric acid. Ziegler et al. (Annalen der Chemie, vol. 473, page 35; 1929) prepared α,β-diphenylheptanoic acid by reacting stilbene with butyl lithium in ether and treating the reaction mixture with carbon dioxide. In certain instances, it is most advantageous to employ the method of Earl and Wilson, (J. Proc. Roy. Soc. N. S. Wales, vol. 65, pages 178 et seq.; 1932). By this method an α,β-dibromoalkanoic acid of the type



is reacted with an appropriate lower aromatic hydrocarbon such as benzene, toluene, xylene, and the like in the presence of aluminum bromide.

α,β-Diarylalkanoyl halides

The acid halides of the aforementioned acids are prepared in the usual manner. Thus a mix-

ture of 440 parts of α,β-diphenylbutyric acid, 660 parts of thionyl chloride and 6400 parts of carbon tetrachloride is refluxed on the steam bath for three hours. The excess volatile reagents are removed under vacuum leaving a crystalline yellow residue of α,β-diphenylbutyryl chloride which may be used without further purification or recrystallized once from petroleum ether to yield a white powder, melting at about 137–141° C.

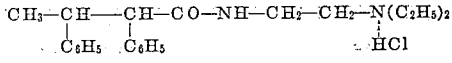
N-dialkylaminoalkyl-α,β-diarylalkanoamides

These amides are prepared by reacting the above acid halides in an inert anhydrous organic solvent with a dialkylaminoalkylamine of the type

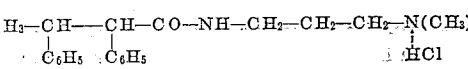
$$H_2N—A—NR'R''$$

All symbols are defined as hereinabove.

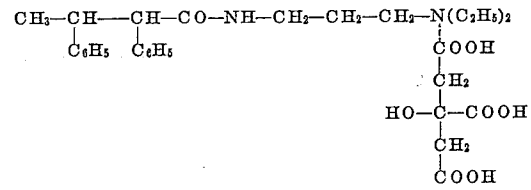
Thus, the N-(β-diethylaminoethyl)-α,β-diphenylbutyramide is prepared as follows. The acid chloride from 400 parts of α,β-diphenylbutyric acid is taken up in 700 parts of anhydrous ethyl ether. To this solution 200 parts of β-diethylaminoethylamine are slowly added with stirring. The tacky white precipitate is extracted with water and the extract is separated and made alkaline with potassium hydroxide. The released base is ether extracted, the extract is dried over anhydrous potassium carbonate, filtered and the ether removed on the steam bath. The N-(β-diethylaminoethyl)-α,β-diphenylbutyramide is obtained as a syrup which crystallizes on standing. It is converted to the hydrochloride by dissolving in anhydrous ether and adding an equivalent of a 10% hydrogen chloride-isopropanol solution. The precipitated hydrochloride is recrystallized from butanone to yield white, water-soluble crystals melting at 159–161° C. The product has the structural formula:



N-(γ-dimethylaminopropyl)-α,β-diphenylbutyramide is prepared by the same procedure. It is obtained as a crystalline residue by evaporation of the ether extract. This residue is further purified by recrystallization from petroleum ether or by vacuum distillation. In the latter case it is distilled at 221–229° C. and 0.5 mm. pressure. On cooling it sets to a solid melting at about 95–100° C. The hydrochloride, prepared as above, consists of white, water-soluble crystals melting at about 171–174° C. This salt has the structural formula:

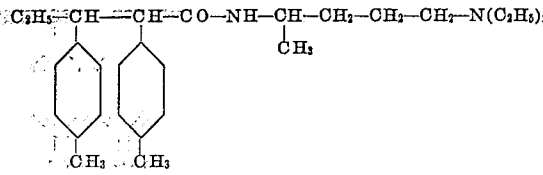


The N-(γ-diethylaminopropyl)-α,β-diphenylbutyramide is prepared by stirring a solution of 250 parts of α,β-diphenylbutyryl chloride in 3500 parts of anhydrous ether and adding slowly 125 parts of γ-diethylaminopropylamine. The tacky white precipitate is extracted with water and the extract is separated and made alkaline. The released base is ether extracted, the extract dried over anhydrous potassium carbonate, and the ether removed by distillation on the steam bath. The N-(γ-diethylaminopropyl)-α,β-diphenylbutyramide is obtained as a syrup which crystallizes on standing. It may be rendered water-soluble by treatment with an equivalent of a 10% citric acid solution. The product has the structural formula:

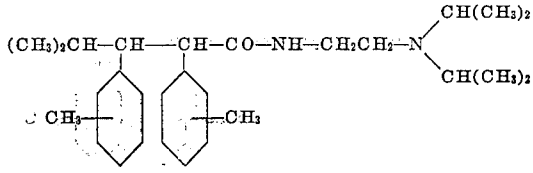


By the same procedure, the following amides are prepared:

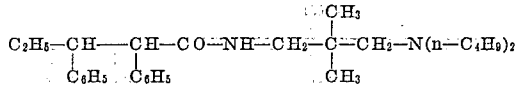
N-(δ-diethylamino-α-methylbutyl)-α,β-di-(p-tolyl)-valeramide of the structural formula



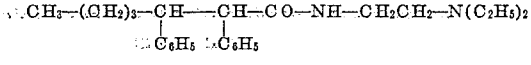
A mixture of N-(β-diisopropylaminoethyl)-α,β-ditolylisocaproamides of the structural formula



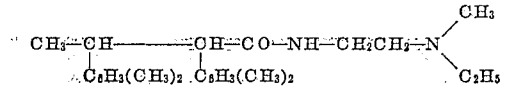
N-(γ-dibutylamino-β,β-dimethylpropyl)-α,β-diphenylvaleramide of the structural formula:



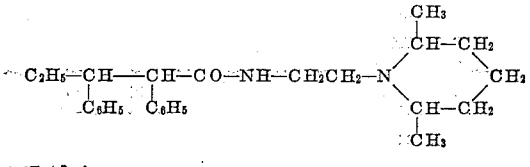
N-(β-diethylaminoethyl)-α,β-diphenylheptanoamide of the structural formula:



N-(β-methylethylaminoethyl)-α,β-dixylylbutyramide of the structural formula:

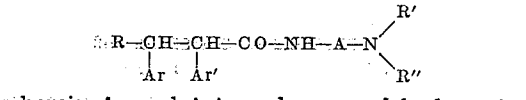


N-β-(1-lupetidino)ethyl-α,β-diphenylvaleramide of the structural formula:



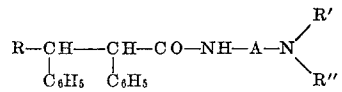
I claim:

1. The new group of organic compounds consisting of the N-dialkylaminoalkyl-α,β-diarylalkanoamides of the structural formula



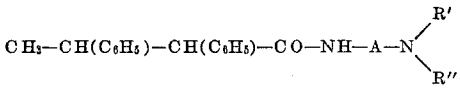
wherein Ar and Ar' are lower aryl hydrocarbon radicals containing 6 to 8 carbon atoms, A is a lower alkylene radical containing at least two carbon atoms, and R, R' and R'' are lower alkyl radicals.

2. The N-dialkylaminoalkyl - α,β - diphenylalkanoamides of the structural formula



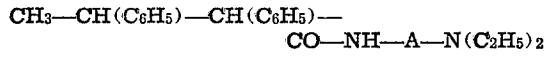
wherein A is a lower alkylene radical containing at least two carbon atoms, and R, R′ and R″ are lower alkyl radicals.

3. The N-dialkylaminoalkyl - α,β - diphenylbutyramides of the structural formula



wherein A is a lower alkylene radical containing at least two carbon atoms, and R′ and R″ are lower alkyl radicals.

4. The N-diethylaminoalkyl - α,β - diphenylbutyramides of the structural formula



wherein the radical A is a lower alkylene radical containing at least two carbon atoms.

5. N-(β-diethylaminoethyl) - α,β - diphenylbutyramide.

6. N-(γ - diethylaminopropyl) -α,β-diphenylbutyramide.

7. N-(γ - dimethylaminopropyl) -α,β-diphenylbutyramide.

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Number	Name	Date
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