This invention relates to a new class of N^1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide derivatives of unusual therapeutic properties. More particularly, this invention relates to N^1-acyl-N^1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide represented by the general structural formula:

\[
\text{R} \quad \text{C} = \text{O}
\]

where

\[
\text{R} = \text{CH}_3, \text{H}
\]

represents saturated or unsaturated, straight or branched alkyl or alkenyl groups, such as acetyl, propionyl, isobutyryl, oleyl, palmityl and pelargonyl, and substituted alkyl groups, such as phenylacetyl, glycylation and glycolyl, or aromatic acyl groups having not in excess of 8 carbon atoms, such as benzoyl and p-aminobenzoacyl.

Preferably, the compounds of this invention are the compounds of the above structural formula where

\[
\text{R} = \text{CH}_3
\]

represents an alkyl or alkenyl group. As a practical matter the N^4-acyl group must be the acyl portion of a nontoxic acid. The lower saturated alkyl (preferably of from 2 to 6 carbon atoms) derivatives are of particular advantage. The alkyl group (R) is advantageously chosen of low molecular weight so that the proportion of active N^1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide released per dosage unit of drug is high, thereby enabling administration of large amounts of active medication in a dosage form of convenient size for the patient. In this regard the compound where R represents methyl is the compound of choice.

The compounds of this invention have utility as chemotherapeutic agents, particularly as antibacterial agents active against both Gram positive and Gram negative organisms. Exemplary of such organisms are Micrococcus pyogenes var. aures, Micrococcus pyogenes var. albus, Streptococcus pyogenes, Diplococcus pneumoniae, Escherichia coli, Aerobacter aerogenes, Proteus vulgaris, and Salmonella typhosa. Further, these compounds have particularly favorable characteristics which make them valuable in medical practice.

N^1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide is excreted rapidly from the body. This necessitates repeated doses of the drug to provide adequate therapeutic effect. The compounds of this invention have been found to give prolonged blood and urine levels of active medication upon oral administration.

The "sulfa" family of chemotherapeutic agents is generally accepted to be detoxified in vivo by acetylation on the N^4 atom. These N^4 compounds are inactive biologically. Contrariwise, the synthetic N^1-acyl derivatives which are the object of this invention are antibacterially active on ingestion and give sustained therapeutic blood levels of N^1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide. It is readily apparent to one skilled in the art that a drug form that gives prolonged therapeutic blood levels is of great advantage in medical practice. This unexpected property of the compounds of this invention enables the doctor to administer the drug, for example, twice a day rather than at four or six-hour intervals. The great advantage of such a dosage regimen is the security of therapeutic blood levels twenty-four hours a day with two doses. Another important advantage is convenience to the patient. A sustained blood level of active medication is maintained rather than the "peak and valley" effect of the multiple daily administration of current medical practice.

Further, these compounds are quite palatable when compared with the disagreeable taste of the parent compound, N^1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide. Therefore, the drug may be administered by preparing suitable pharmaceutical forms, such as tablets or suspensions for oral use.

The compounds of this invention are prepared by reacting N^1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide with an acetylation agent, preferably an acyl anhydride, in the presence of an inorganic or a tertiary organic base such as pyridine, collidine, tributylamine or sodium carbonate in an inert organic solvent for the sulfanilamide such as dimethylformamide, water, acetone or a water-acetone mixture, preferably at relatively low temperatures, for instance from 0-30°C. It is apparent that the base may be present in equimolar quantities or in excess. In the latter case, the base may serve as the reaction medium as well. Since the N^1-acyl derivatives in solution tend to rearrange to the N^4 atom under the influence of heat, the use of hot solvents during the preparation of the N^4-acyl derivatives should be avoided.

The compounds of this invention are also prepared by acetylation the N-(5-ethyl-1,3,4-thiadiazole-2-yl)-4-nitrobenzenesulfonamide with an acyl halide or acyl anhydride in an inert organic solvent for the sulfonamide, for example, acetone or dimethylformamide, with conditions which may be more forcing than those described previously, such as for example, at temperatures of 130°C. Of course this wider range of reaction conditions, namely using higher temperature and the more reactive acyl halides, are applicable since the possibility of N^4-acetylation is not present. The base may be present in equimolar quantities or in excess. In the latter case the base may serve as the reaction medium as well. The resulting N-acyl-N^1-(5-ethyl-1,3,4-thiadiazole-2-yl)-4-nitrobenzenesulfonamide is reduced under mild reduction conditions to the desired N^1-acyl-N^1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide, for example, by catalytic reduction using Adams's catalyst or palladium-on-charcoal in an alcoholic medium, such as in ethanol or methanol at low pressures and temperatures. This method is particularly advantageous where acetylation at the N^1 position of N^1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide is more difficult due to RC=O in the foregoing structural formula being a particularly bulky group, such as a tertiary butyryl or benzoyl moiety.

Alternatively, the N^1-acyl compounds of this invention can be prepared from the sodium, potassium or silver salt of N^1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide by reaction with an appropriate acyl halide in an inert organic solvent for the sulfanilamide such as acetone, acetonitrile or dimethylacetamide.

The methods of preparing the compounds of this invention will be readily apparent from the following examples:
Example I
A suspension of 113.6 g. of N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide in a mixture of 1 l. of acetone and 1 l. of water is stirred with 26 ml. of strong ammonia water until a complete solution is attained. The solution is cooled to 0–10° C. and 51 g. of acetic anhydride is added rapidly dropwise. After thirty minutes in the cold, the desired product crystallizes from solution. The product is separated by filtration, washed with water and cold ethanol to give white crystals of N1-acetyl-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide; M. P. 220–221° C. after preliminary gathering at 137–138° C. The product may be recrystallized from aqueous acetone if desired.

Example II
A suspension of 31.6 g. of the sodium salt of N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide (prepared by reacting the sulfonamide with one equivalent of sodium hydroxide solution, evaporating the water by freeze-drying and using the salt at once) in 200 ml. of acetone with 12 ml. of tributylamine is stirred vigorously while 14.0 g. of benzoyl chloride is added dropwise over a two-hour period. The crystalline product is obtained by quenching in water and then washing the precipitate with water to remove the admixed sodium chloride. The crude product, N1-benzoyl-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide, is purified by recrystallization from a benzene-dimethylformamide mixture.

Example III
A suspension of 32 g. of N-(5-ethyl-1,3,4-thiadiazole-2-yl)-4-nitrobenzenesulfonamide in 150 ml. of pyridine is swirled at 13 g. of pivalyl chloride is added dropwise. After standing at room temperature for twelve hours, the reaction mixture is quenched in a large excess of water. The crude solid, N-trimethylacetonyl-N-(5-ethyl-1,3,4-thiadiazole-2-yl)-4-nitrobenzenesulfonamide, is then suspended in 200 ml. of ethanol with 5% palladium-on-charcoal and hydrogenated at room temperature and 50 p.s.i. The resulting solution is then filtered. The solid thusly obtained is extracted with acetone. After concentrating the combined alcohol-acetone filtrates by evaporation under reduced pressure, a crystalline solid, N1-trimethylacetonyl-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide, is obtained.

Example IV
A suspension of 14.2 g. of N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide in 50 ml. of acetone is acylated with 6.5 g. of propionic anhydride in dimethylformamide with 6 ml. of pyridine at 0–5° C. The crystalline product, N1-propanoyl-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide, is obtained by quenching the reaction mixture in water and recrystallizing the precipitate from aqueous acetone; M. P. 219–221° C. after preliminary melting at 59–101° C.

Example V
A suspension of 26.4 g. of crude oleoyl anhydride (prepared by reacting 29 g. of oleic acid with 15 g. of acetic anhydride and removing the volatiles in vacuo) and 14.2 g. of N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide is reacted according to the process of Example I to give N1-oleoyl-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide after titration with isocitric in the cold.

Example VI
N1-butyryl-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide is prepared from 14.2 g. of N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide and 7.9 g. of butyric anhydride as in Example I to give white crystals; M. P. 219–221° C. after preliminary melting at 120–122° C.

Example VII
N1-phenylacetonyl-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide is prepared from 28.4 g. of N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide and 25.4 g. of phenylacetic anhydride as in Example I, but using 4 ml. of pyridine as a base. The crude product is recrystallized from a benzene-dimethylformamide mixture.

Example VIII
A solution of 21.4 g. of carbobenzoxycarbonyl chloride in dry ethyl ether is added dropwise to a stirred suspension of 31.4 g. of N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-4-nitrobenzenesulfonamide in 150 ml. of dried ethyl acetate with 9 ml. of pyridine. The reaction mixture is concentrated in vacuo and cooled. The resulting precipitate is then separated, washed with water and dried in vacuo.

The crude N-carbobenzoxy-N1-phenylacetyl-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-4-nitrobenzenesulfonamide is suspended in 550 ml. of ethanol and hydrogenated at low pressure and temperature in the presence of palladium black catalyst. The catalyst is separated by filtration. Concentrating the filtrate and cooling yields a white solid, N1-glyceryl-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide by fractional crystallization.

Example IX
N1-isobutyrin-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide is prepared from 14.2 g. of N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide and 7.9 g. of isobutyryl anhydride as in Example I to give white crystals from aqueous acetone; M. P. 219–221° C. after preliminary melting at 124–125° C.

Example X
N1-stearoyl-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide is prepared from 14.2 g. of N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide and 27.5 g. of crude stearic anhydride as in Example V to give white crystals from an isocitrate-acetone mixture.

Example XI
N1-caproyl-N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide is prepared from 28.4 g. of N1-(5-ethyl-1,3,4-thiadiazole-2-yl)-sulfanilamide and 21.4 g. of n-caproyl anhydride as in Example I but using tributyl anine as the basic reactant to give white crystals from aqueous acetone.

What is claimed is:
1. Compounds represented by the following formula:

![Chemical Structure Image]

in which

2. Compounds in accordance with claim 1 characterized in that

3. Compounds in accordance with claim 1 characterized in that
4. Compounds in accordance with claim 1 characterized in that
\[ R \bigcap \bigcirc = \bigcirc \bigcirc \]
is butyryl.

5. Compounds in accordance with claim 1 characterized in that
\[ R \bigcap \bigcirc = \bigcirc \bigcirc \]
is isobutyryl.

6. Compounds in accordance with claim 1 characterized in that
\[ R \bigcap \bigcirc = \bigcirc \bigcirc \]
is caproyl.

7. Compounds in accordance with claim 1 characterized in that
\[ R \bigcap \bigcirc = \bigcirc \bigcirc \]
is saturated alkanoyl having from 2 to 6 carbon atoms.

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