

HYPOGLYCEMIC 5-SUBSTITUTED OXAZOLIDINE-2,4-DIONES

The present invention relates to certain 5-furyl, 5-thienyl, 5-chromanyl, 2,3-dihydrobenzo[b]furanyl, 5-pyridyl, 5-quinolyl, 5-pyrrolyl, 5-indolyl, 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl and 5-isoxazolyl derivatives of oxazolidine-2,4-dione having utility as hypoglycemic agents.

In spite of the early discovery of insulin and its subsequent wide-spread use in the treatment of diabetes, and the later discovery and use of sulfonyl-ureas (e.g., chlorpropamide, tolbutamide, acetohexamide, tolazamide) and biguanides (e.g., phenformin) as oral hypoglycemic agents, the treatment of diabetes remains less than satisfactory. The use of insulin, necessary in a high percentage of diabetics where available synthetic hypoglycemic agents are not effective, requires multiple daily, usually self, injection. Determination of the proper dosage of insulin requires frequent estimations of the sugar in the urine or in the blood. The administration of an excess dose of insulin causes hypoglycemia, with effects ranging from mild abnormalities in blood glucose to coma, or even death. Where effective, a synthetic hypoglycemic agent is preferred over insulin, being more convenient to administer and less prone to cause severe hypoglycemic reactions. However, the clinically available hypoglycemics are unfortunately fraught with other toxic manifestations which limit their use. In any event, where one of these agents may fail in an individual case, another may succeed. A continuing need for hypoglycemic agents, which may be less toxic or succeed where others fail, is clearly evident.

In addition to the hypoglycemic agents cited above, a variety of other compounds have been reported to possess this type of activity, as reviewed recently

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by Blank [Burger's Medicinal Chemistry, Fourth Edition, Part II, John Wiley and Sons, N.Y. (1979), pp. 1057-1080].

The oxazolidine-2,4-diones of the present invention are novel compounds; this in spite of the fact that the oxazolidine-2,4-diones are broadly known as a class of compounds [for an extensive review, see Clark-Lewis, Chem. Rev. 58, pp. 63-99 (1958)]. Among the compounds known in this class are 5-phenyloxazolidine-2,4-dione, variously reported as an intermediate to certain beta-lactam antibacterial agents (Sheehan, U.S. Patent 2,721,197), as an anti-depressant agent (Plotnikoff, U.S. Patent 3,699,229) and as an anticonvulsant agent [Brink and Freeman, J. Neuro. Chem. 19 (7), pp. 1783-1788 (1972)]; a number of 5-phenyloxazolidine-2,4-diones substituted on the phenyl ring, e.g., 5-(4-methoxyphenyl)oxazolidine-2,4-dione [King and Clark-Lewis, J. Chem. Soc., pp. 3077-3079 (1961)], 5-(4-chlorophenyl)oxazolidine-2,4-dione [Najer et al., Bull. soc. chim. France, pp. 1226-1230 (1961)], 5-(4-methylphenyl)oxazolidine-2,4-dione [Reibsoner et al., J. Am. Chem. Soc. 61, pp. 3491-3493 (1939)], and 5-(4-aminophenyl)oxazolidine-2,4-dione (German Patent 108,026); and 5-(2-pyrryl)-oxazolidine-2,4-dione [Ciamacian and Silber, Gazz. chim. ital. 16, 357 (1886); Ber. 19, 1708-1714 (1886)]. The last-named compound, having no prior known utility, shows only relatively weak hypoglycemic activity (vide post, Table I).

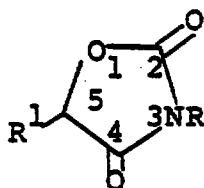
Oxazolidine-2,4-dione and substituted oxazolidine-2,4-diones (specifically, the 5-methyl and 5,5-dimethyl derivatives) have been reported as acid moieties suitable for forming acid-addition salts with the hypoglycemic, basic biguanides (Shapiro and Freedman, U.S. Patent 2,961,377). We have determined

that neither oxazolidine-2,4-dione itself, nor 5,5-dimethyloxazolidine-2,4-dione possess the hypoglycemic activity of the compounds of the present invention.

Recently, a group of spiro-oxazolidine-2,4-dione derivatives have been reported which are aldose reductase inhibitors, thus finding utility in the treatment of certain complications of diabetes (Schnur, U.S. Patent 4,200,642).

A process for the synthesis of 3-aryloxazolidine-2,4-diones (wherein said aryl group is 6 to 12 carbon atoms, unsubstituted or substituted with one or more halogen atoms, methyl or methoxy) is the subject of another recent U.S. Patent (Scholz, U.S. 4,220,787). The utility of these compounds is not specified.

The present invention is concerned with compounds of the formula



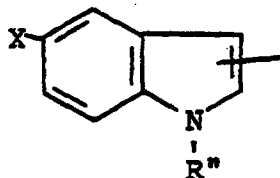
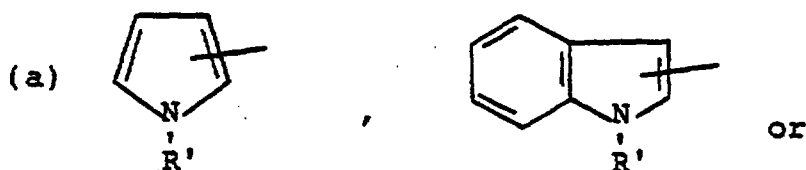
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wherein

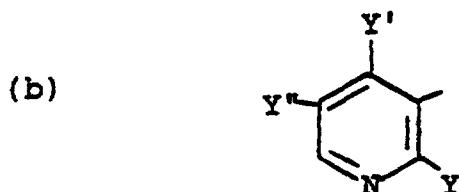
R is hydrogen, (C₁-C₄)-alkanoyl (e.g., formyl, acetyl, isobutyryl), benzoyl, (C₂-C₄)-carbalkoxy (e.g., carbomethoxy, carbethoxy, carboisopropoxy), (C₁-C₃)-alkylcarbamoyl (e.g., N-methylcarbamoyl, N-propylcarbamoyl), (C₅-C₇)-cycloalkylcarbamoyl (e.g., N-cyclohexylcarbamoyl) or di-(C₁-C₃)-dialkylcarbamoyl (e.g., N,N-dimethylcarbamoyl); and

R¹ is:

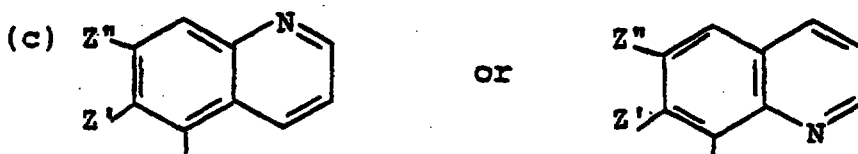
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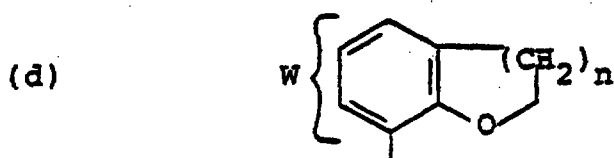
wherein R' is (C₁-C₄)alkyl or phenyl, R'' is hydrogen, (C₁-C₄)alkyl or phenyl and X is halo (fluoro, chloro, bromo or iodo); these formulae are intended to encompass 2- or 3-pyrrolyl and indolyl derivatives, with substituents as specified;



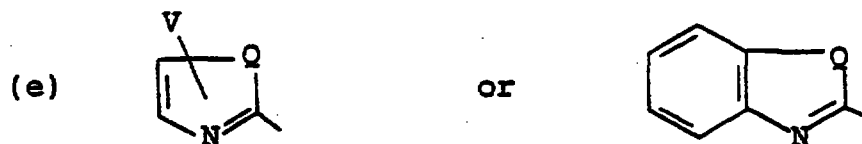
wherein Y is hydrogen or (C₁-C₃)alkoxy, Y' is hydrogen or (C₁-C₃)alkyl and Y'' is hydrogen or halo;



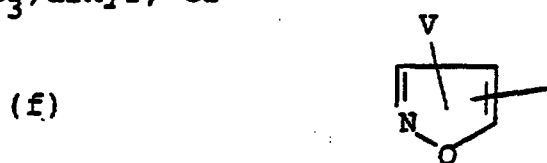
wherein Z' is hydrogen, halo or (C₁-C₃)alkoxy and Z'' is hydrogen or halo;



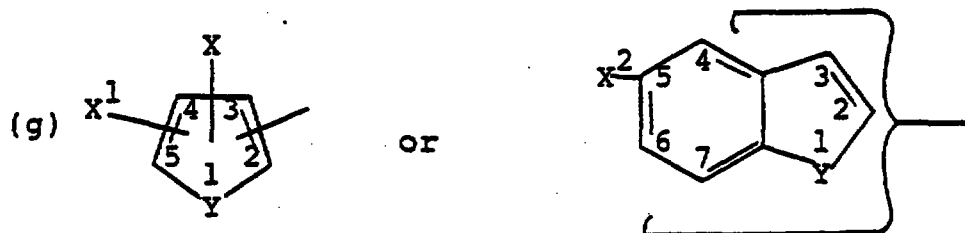
wherein W is hydrogen or halo, and n is 1 or 2; these formula are intended to encompass 6- or 7-halo-8-chromanyl or 5- or 6-halo-7-benzofuranyl derivatives;



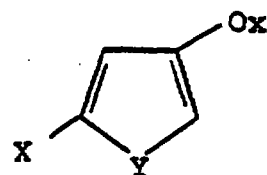
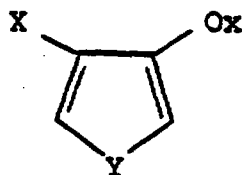
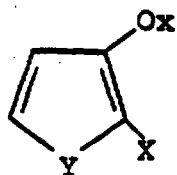
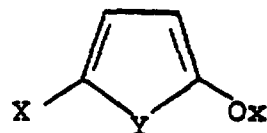
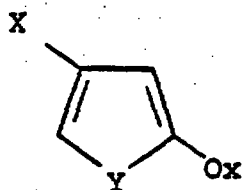
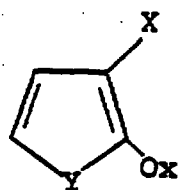
5 wherein Q is sulfur or oxygen and V is hydrogen or (C₁-C₃)alkyl; or



wherein Q is sulfur or oxygen; and V is hydrogen or (C₁-C₃)alkyl; these formula are intended to encompass
10 3-, 4- and 5-isothiazolyl and isoxazolyl derivatives;



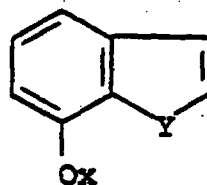
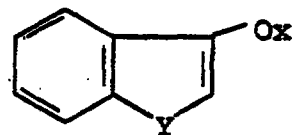
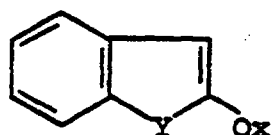
wherein Y is sulfur or oxygen; X is hydrogen, fluoro, chloro, bromo, iodo, methyl, phenyl, benzoyl or (C₁-C₃)-alkoxy; X¹ is hydrogen or methyl; and X² is hydrogen, fluoro, chloro, bromo or iodo; when X¹ is hydrogen, the first formula is intended to encompass the full gamut of 5-(2-furyl)-, 5-(3-furyl)-, 5-(2-thienyl)- and 5-(3-thienyl)-derivatives of oxazolidine-2,4-dione wherein the substituent X can be attached to
15
20 any vacant carbon position of the furan/thiophene ring, i.e.,



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where X and Y are as defined above and Ox is used as an abbreviation for the oxazolidin-2,4-dione ring attached at the 5-position; when both X and X¹ are other than hydrogen, the second substituent can be inserted at either vacant position in any one of these six variants; the second formula is intended to encompass those compounds wherein the oxazolidine is substituted at the 2-, 3- or 7-position of the benzo[b]furan/benzo[b]thiophene ring system, i.e.

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The invention also encompasses the pharmaceutically acceptable cationic salts of compounds of the formula (1) when R is hydrogen, as well as the pharmaceutically acceptable acid addition salts thereof when R¹ contains a basic nitrogen function.

It is believed that the inherent, high activity of these compounds resides primarily in those compounds wherein R is hydrogen, and that those compounds wherein R is one of a variety of carbonyl derivatives defined above represent so-called pro-drugs, i.e., the carbonyl side chain is removed by hydrolysis under physiological conditions, yielding the fully-active compounds wherein R is hydrogen.

The expression "pharmaceutically acceptable cationic salts" is intended to define such salts as the alkali metal salts, (e.g., sodium and potassium), alkaline earth metal salts (e.g., calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol), procaine, etc.

The expression "pharmaceutically acceptable acid addition salts" is intended to include such salts as the hydrochloride, hydrobromide, hydroiodide, nitrate, hydrogen sulfate, dihydrogen phosphate, mesylate, maleate, succinate, etc.

The compounds of the present invention possess hypoglycemic activity, reflecting their clinical utility in the lowering of the blood glucose level of hyperglycemic mammals, including man, to normal values. They have the special advantage of lowering

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blood glucose values to a normal range without danger of causing hypoglycemia. The compounds of the present invention are tested for hypoglycemic (anti-hyperglycemic) activity in rats, using the so-called glucose tolerance test, as described in greater detail hereinafter.

Preferred compounds, because of their better hypoglycemic activity, are those wherein R is hydrogen, or the pharmaceutically acceptable salts thereof.

Among those compounds of the formula (1) wherein R is hydrogen, the most preferred compounds, because of their excellent hypoglycemic activity, are:

- 5-(1-methyl-2-pyrrolyl)oxazolidine-2,4-dione;
- 5-(1-ethyl-2-pyrrolyl)oxazolidine-2,4-dione;
- 5-(1-phenyl-2-pyrrolyl)oxazolidine-2,4-dione;
- 5-(2-methoxy-3-pyridyl)oxazolidine-2,4-dione;
- 5-(2-ethoxy-3-pyridyl)oxazolidine-2,4-dione;
- 5-(5-chloro-2-methoxy-3-pyridyl)oxazolidine-2,4-dione;
- 5-(5-chloro-2-ethoxy-3-pyridyl)oxazolidine-2,4-dione;
- 5-(8-quinolyl)oxazolidine-2,4-dione;
- 5-(7-methoxy-8-quinolyl)oxazolidine-2,4-dione;
- 5-(6-chloro-8-quinolyl)oxazolidine-2,4-dione;
- 5-(6-fluoro-8-quinolyl)oxazolidine-2,4-dione;
- 5-(2-benzthiazolyl)oxazolidine-2,4-dione;
- 5-(2-thiazolyl)oxazolidine-2,4-dione;
- 5-(6-chloro-8-chromanyl)oxazolidine-2,4-dione;
- 5-(6-fluoro-8-chromanyl)oxazolidine-2,4-dione;
- 5-(5-chloro-2,3-dihydro-7-benzofuranyl)oxazolidine-2,4-dione;
- 5-(3-methyl-5-isoxazolyl)oxazolidine-2,4-dione;
- 5-(3-thienyl)oxazolidine-2,4-dione;

5-(4-bromo-3-thienyl)oxazolidin-2,4-dione;
5-(4-ethoxy-3-thienyl)oxazolidin-2,4-dione;
5-(4-ethoxy-2-methyl-3-thienyl)oxazolidin-2,4-
dione;
5 5-(4-methoxy-2-methyl-3-thienyl)oxazolidin-2,4-
dione;
5-(3-methyl-2-thienyl)oxazolidin-2,4-dione;
5-(3-methoxy-2-thienyl)oxazolidin-2,4-dione;
5-(3-furyl)oxazolidin-2,4-dione;
10 5-(2-furyl)oxazolidin-2,4-dione;
5-(3-bromo-2-furyl)oxazolidin-2,4-dione;
5-(5-chloro-2-furyl)oxazolidin-2,4-dione;
5-(7-benzo[b]thienyl)oxazolidin-2,4-dione; and
5-(5-chloro-7-benzo[b]furyl)oxazolidin-2,4-
15 dione.

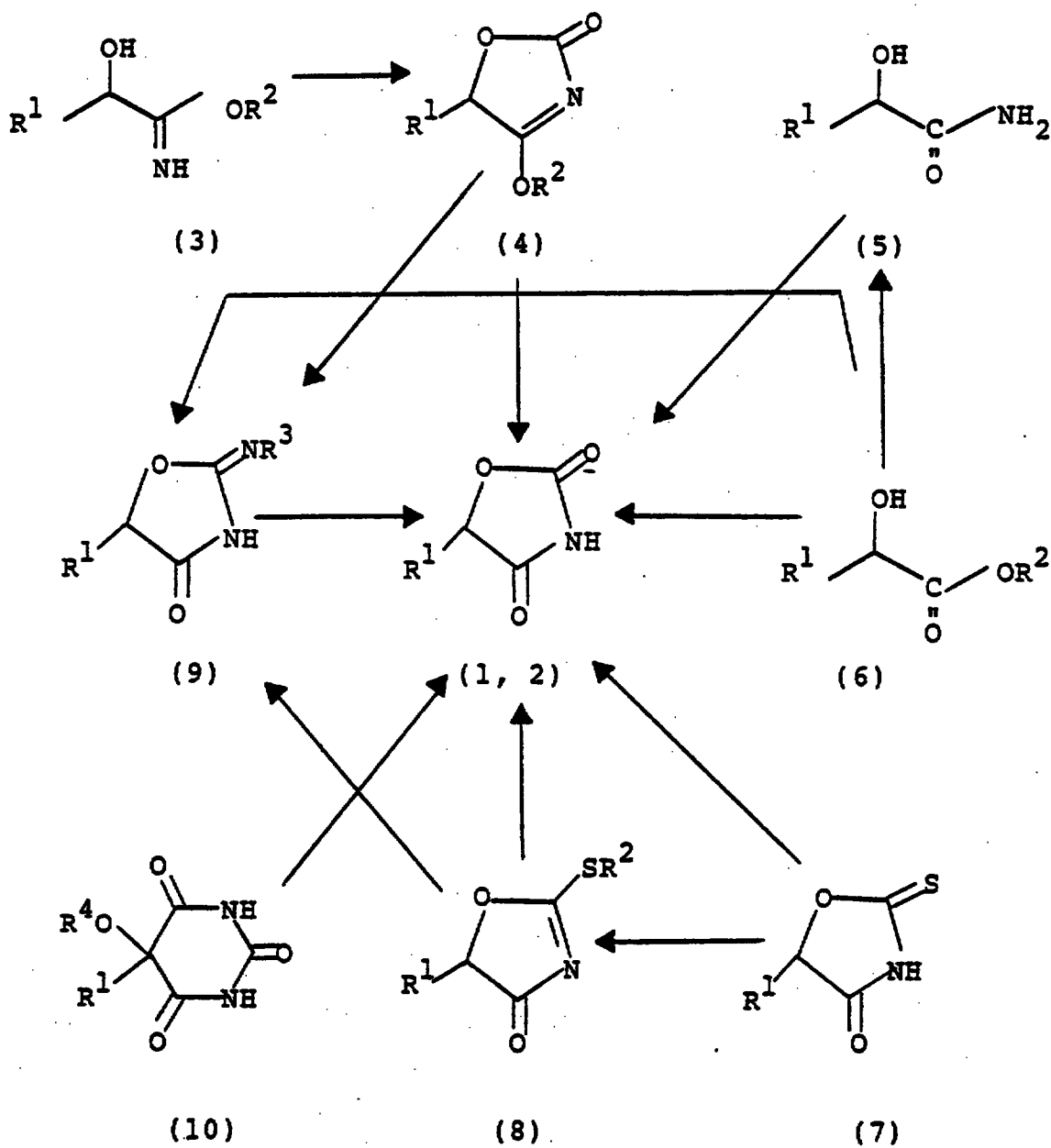
The compounds of the present invention are prepared by a variety of methods, as summarized in Flow-sheet I, wherein

20 R^1 is as defined above;
 R^2 is lower alkyl (e.g. methyl or ethyl);
 R^3 is hydrogen, lower alkyl or phenyl; and
 R^4 is hydrogen, or acyl such as acetyl or benzoyl.

25 A particularly convenient synthesis for compounds of the present invention is via carboximide (3). The latter compound is reacted with phosgene in an inert solvent such as tetrahydrofuran in the presence of 2 to 2.3 equivalents of a tertiary amine (e.g. triethylamine, N-methylmorpholine). A further equivalent
30 of tertiary amine is used if the carboximide is introduced as the acid addition salt (e.g. hydrochloride salt). The temperature of the reaction is not critical, but lower temperatures (e.g. -10° to 10°C.) are preferred during the initial stages of the

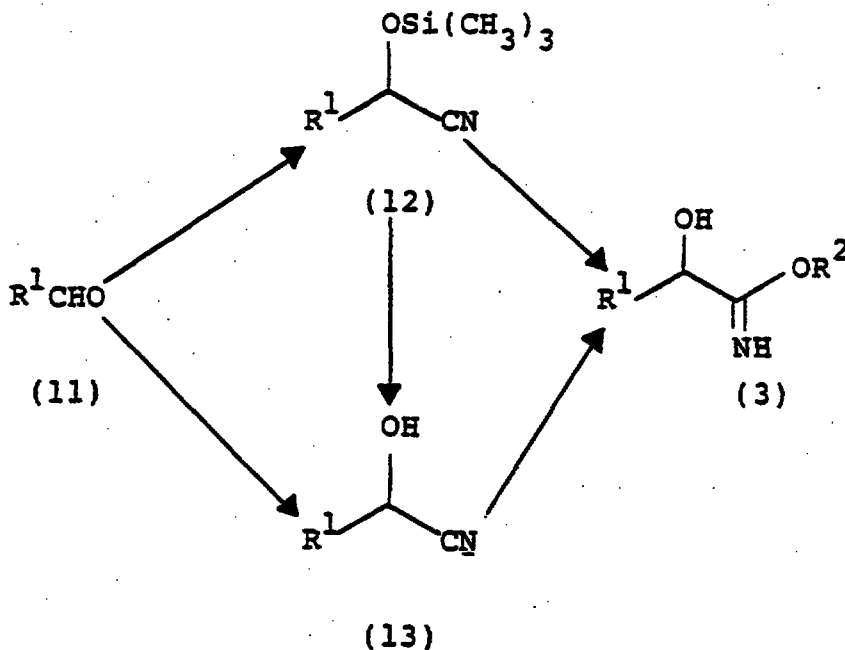
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Flowsheet I
Oxazolidine-2,4-dione Precursors



reaction, particularly if it is desired to isolate the intermediate 4-alkoxyoxazol-2-one (4). Isolation of this intermediate is carried out by simple evaporation of the reaction mixture to dryness. On further
5 reaction at higher temperatures (e.g. 20°-150°C.) or on aqueous work-up the intermediate (4) is converted to the desired oxazolidine-2,4-dione. When a primary or secondary amine function is desired in the final product, this functionality is introduced via an
10 oxazolidine-2,4-dione containing a group selectively reducible (e.g. by catalytic hydrogenation or acid/metal couple) to the primary or secondary amine. For example an N-benzylindole can be used as a precursor for an indole derivative.

The carboximide (3) is conveniently prepared from the corresponding aldehyde by the sequence:



The aldehyde (11) is converted to the cyanohydrin (13) by standard procedures (e.g. via the bisulfite adduct, which is reacted with cyanide in a two phase, aqueous-organic solvent system). Alternatively, the aldehyde is converted to the trimethylsilyl cyanohydrin (12) by reaction with trimethylsilylcarbonitrile in the presence of a catalytic quantity of a Lewis acid, e.g., zinc iodide. A reaction inert solvent (e.g. methylene chloride, ether) is generally used when the aldehyde is a solid, but is optional when the aldehyde is a liquid. The temperature of the reaction is not critical, it being conveniently made up at reduced temperature (e.g. 0-5°C.) and allowed to proceed at room temperature for a matter of hours or days, as necessary to achieve complete reaction. If desired, the trimethylsilyl ether can be hydrolyzed to cyanohydrin, conveniently at reduced temperature (e.g. -10°C.) in a two phase strong aqueous acid/organic solvent system.

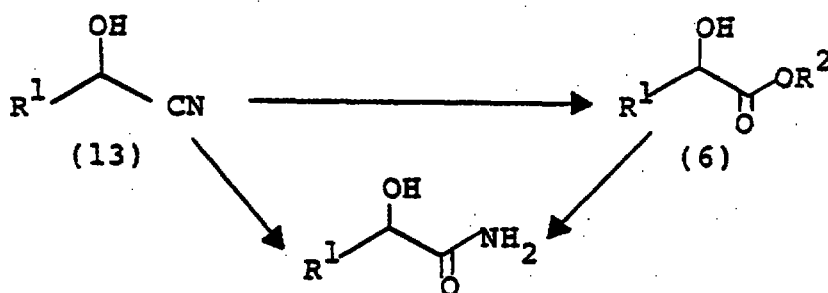
Either the cyanohydrin (13) or the trimethylsilyl ether (12) is converted to the carboximide (3) by strong acid catalyzed alcoholysis (using strictly anhydrous conditions). A convenient method is to
5 simply dissolve the nitrile in alcohol which has been saturated with hydrogen chloride) and allow the solution to stand until carboximide formation is complete. Temperature is not critical, although lower temperatures (e.g. 0-25°C.) generally lead to
10 more optimal yields.

The aldehydes required for the above syntheses are broadly available either commercially, or by literature methods. For example, N-alkylpyrrole-2-carbaldehydes are obtained by alkylation of pyrrole-
15 2-carbaldehyde (Weygand, Organic Preparations, Interscience, New York, 1945, p. 403) using conditions specifically exemplified hereinafter for the preparation of N-alkylpyrroles, or by Reimer-Tiemann formylation of N-alkylpyrrole (cf Weygand loc. cit.); 3-formylindoles
20 are similarly obtained from indoles [cf Boyd and Robson, Biochem J. 29, p. 555 (1935; Shabica et al., J. Am. Chem. Soc. 68, p. 1156 (1946))]; Rosenmund hydrogenation of the corresponding acid chloride [e.g. 3-furaldehyde; Hayes, J. Am. Chem. Soc. 71,
25 2581 (1949)], from halomethyl compounds by the Sommelet reaction [e.g. 3-thenaldehyde; Campaigne and LaSuer, J. Am. Chem. Soc. 70, 1557 (1948)], formylation [e.g. 2-thenaldehyde, 3-methyl-2-thenaldehyde, 5-methyl-2-thenaldehyde; Watson and Michaels, J. Am. Chem. Soc.
30 72, 1422 (1950), Organic Syntheses 31, 108 (1951); 3-bromo-2-thenaldehyde; Elliott et al., J. Chem. Soc. (C), 2551 (1971)]; reduction of chloromethyl substituted aldehydes [e.g. 5-methyl-2-furaldehyde, Spence and Wild, J. Chem. Soc., 338 (1935)], oxidation of the
35 corresponding alcohol [e.g. 2-thenaldehyde; Emerson

and Patrick, J. Org. Chem., 14, 790 (1949)], interaction of Grignard reagents with orthoformic esters [e.g. 2-thenaldehyde; Cagniant, Bull. soc. chim. France 16, 849 (1949)], decarboxylation of alpha-keto acids [e.g. 2-thenaldehyde; Barger and Easson, J. Chem. Soc., 2100 (1938)], and halogenation [e.g. 2-bromo-3-thenaldehyde; Elliot et al., loc. cit.]; a variety of the presently required aldehydes are further available by the hydrolysis of gem-dihalides, oxidation of primary alcohols, interaction of Grignard reagents with orthoformic esters and other methods known in the art. Additional methods are noted in the Preparations detailed hereinafter.

Another suitable precursor for those oxazolidine-2,4-diones of the present invention lacking a primary or secondary amine function is the alpha-hydroxy amide (5). The latter compound is converted to the desired oxazolidine-2,4-dione (1), either by reaction with alkyl chloroformate in the presence of a basic catalyst such as potassium carbonate, or by reaction with a dialkyl carbonate in the presence of a more strongly basic catalyst such as sodium methoxide or potassium tert-butoxide. An alcohol is generally suitable as solvent for the latter reaction with 1 to 3 equivalents of both dialkyl carbonate and base employed, preferably 2-3 equivalents of each. When a primary or secondary amine function is desired in the final product, this functionality is introduced via an oxazolidine-2,4-dione containing a suitable precursor group, as described above.

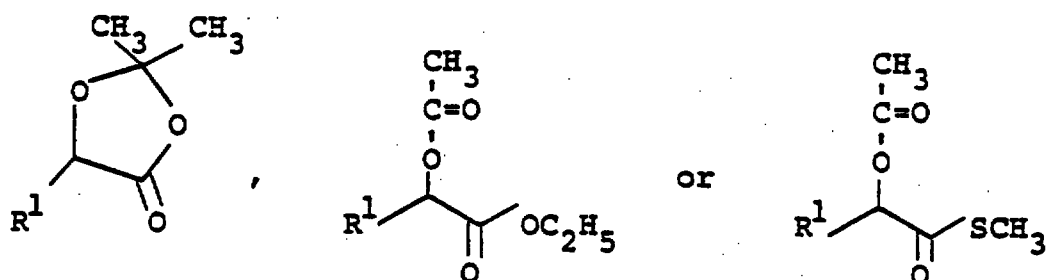
The required alpha-hydroxy amide is conveniently prepared from cyanohydrin (13) or from alpha-hydroxy acid or ester (6):



Convenient conditions for the hydrolysis of the cyanohydrin (13) are to treat the cyanohydrin in formic acid with excess concentrated hydrochloric acid. A temperature range of 0-75°C. is generally satisfactory, depending upon the stability of the individual amide in this medium. If desired, an intermediate formate ester of (5) can be isolated under these conditions. Over hydrolysis to the acid can be avoided by tlc monitoring of the reaction, as detailed below. Convenient conditions for the aminolysis of ester (6) are to simply heat the ester in hot concentrated ammonium hydroxide.

The alpha-hydroxy ester (6) itself can also be employed as the immediate precursor of the desired oxazolidine-2,4-dione. The ester is reacted with urea (or one of certain substituted ureas, such as phenyl urea or 1-acetyl-3-methylurea) in the presence of a basic catalyst such as sodium ethoxide (suitably 1 equivalent) in alcohol at a temperature of 50-110°C. The ester to be used for this purpose is by no means restricted to a simple lower alkyl ester, but can be any one of a broad variety of esters, e.g. phenyl, benzyl, etc. Furthermore, the ester can be replaced by a 1,3-dioxolan-4-one, an alpha-acyloxy ester or a thioester e.g.,

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and the urea can be replaced by a urethan.

Two other precursors suitable for the synthesis of the desired oxazolidine-2,4-diones are the thio compounds (7) and (8). The 2-thioxo compound (7) is converted to the desired oxazolidine-2,4-diones under oxidative conditions, e.g. mercuric ion, aqueous bromine or chlorine, metaperiodate, or aqueous hydrogen peroxide, usually in excess and in the presence of a co-solvent, such as a lower alcohol. The temperature of reaction is not critical, temperatures in the range 25-100°C. being generally satisfactory. Other methods are usually preferred when R¹ has an amine function, since competing oxidation at the nitrogen tends to reduce yields and complicates isolation of the desired product; it has been found, however, that when the product contains a tert-amine (e.g., pyridine, quinoline), that periodate or bromine are reagents well-suited for this purpose. The oxazolidine-2,4-diones are obtained from the alkyl-thio compounds (8) by simple acid or base catalyzed hydrolysis. Preferable conditions are aqueous hydrochloric acid in a temperature range of 0-50°C.

The precursor 2-thioxo compound (7) is prepared from the corresponding aldehyde (11), generally accomplished in an aqueous acidic media by the action of thiocyanate (1-1.1 equivalents) and cyanide (1 to 1.2 equivalents) at 0-70°C., following the method of

Lindberg and Pederson by which method the preparation of 5-(2-thienyl)-2-thioxazolidin-4-one has been reported [Acta Pharm. Suecica 5 (1), pp. 15-22 (1968); Chem. Abstr. 69, 52050k]. The precursor 2-alkylthio compounds (8) can be prepared by alkylation of the 2-thioxo compounds (7), e.g. with an alkyl halide or dialkyl sulfate, preferably in the presence of at least two equivalents of a base such as a lower alkoxide in a reaction inert solvent such as a lower alkanol. The 3-alkyl derivative can be a by-product of this reaction.

Also suitable as a precursor is the 2-imino-oxazolidine-4-one derivative (9), readily hydrolyzed to the oxazolidine-2,4-dione, preferably under aqueous acid conditions. The required 2-iminooxazolidin-4-one is obtained by condensation of the alpha-hydroxy ester (6) with guanidine or with thiourea in the presence of one equivalent of a strong base such as sodium alkoxide, by ammonolysis of the 2-alkoxy compound (isomeric with 4) or the 2-thioalkyl compound (8), by alkali induced cyclization of the appropriate alpha-halogenureides ($R^1CHZCONHCONHR^3$ wherein Z is a halogen such as chloro or bromo), or by the condensation of the appropriate alkyl alpha-haloacetates ($R^1CHZCOOR^2$) with urea or a substituted urea ($R^3NHCONH_2$).

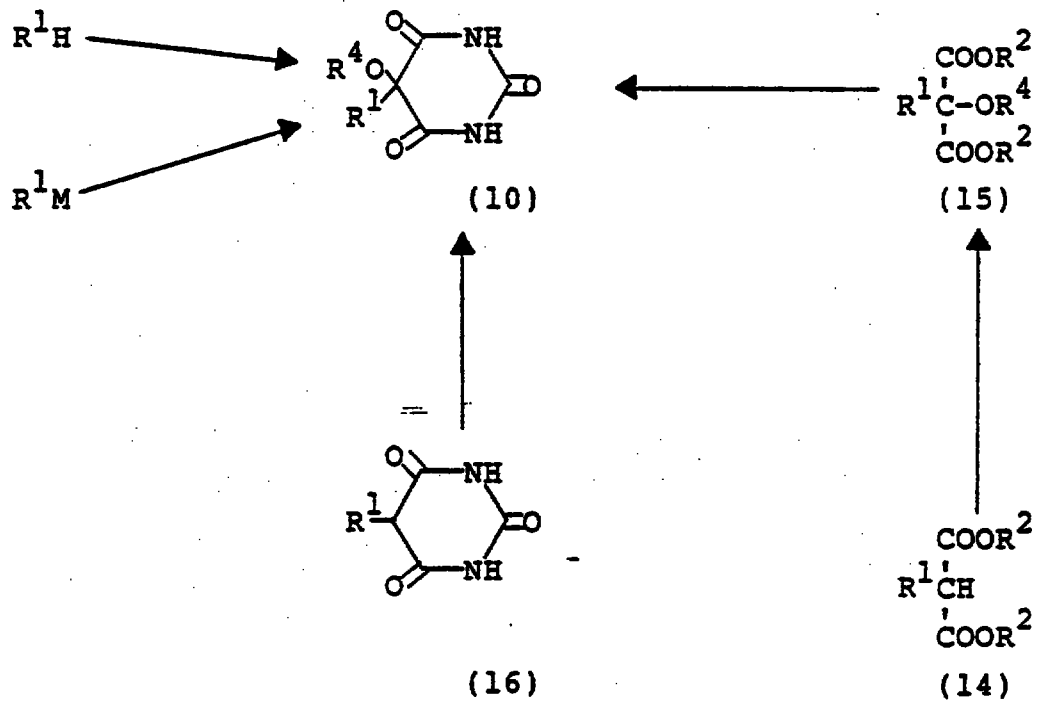
Ammonolysis of the 4-alkoxy derivatives (4) yields 4-imino derivatives (isomeric with 9). The latter compounds are also readily hydrolyzed to oxazolidine-2,4-diones. The 4-alkoxy derivatives themselves are also prepared from the silver salt of the desired oxazolidine-2,4-dione.

Also highly useful as precursors of the oxazolidine-2,4-diones of the present invention are the dialuric acids and acyl dialuric acids (10). These

are readily converted, under mildly basic conditions, to the desired oxazolidine-2,4-diones. Methods suitable for the preparation of precursor dialuric acids (10) are shown in Flowsheet II, wherein the substituents R^1 , R^2 and R^4 are as defined above, and M is Li, MgCl, MgBr, MgI, or other suitable metal.

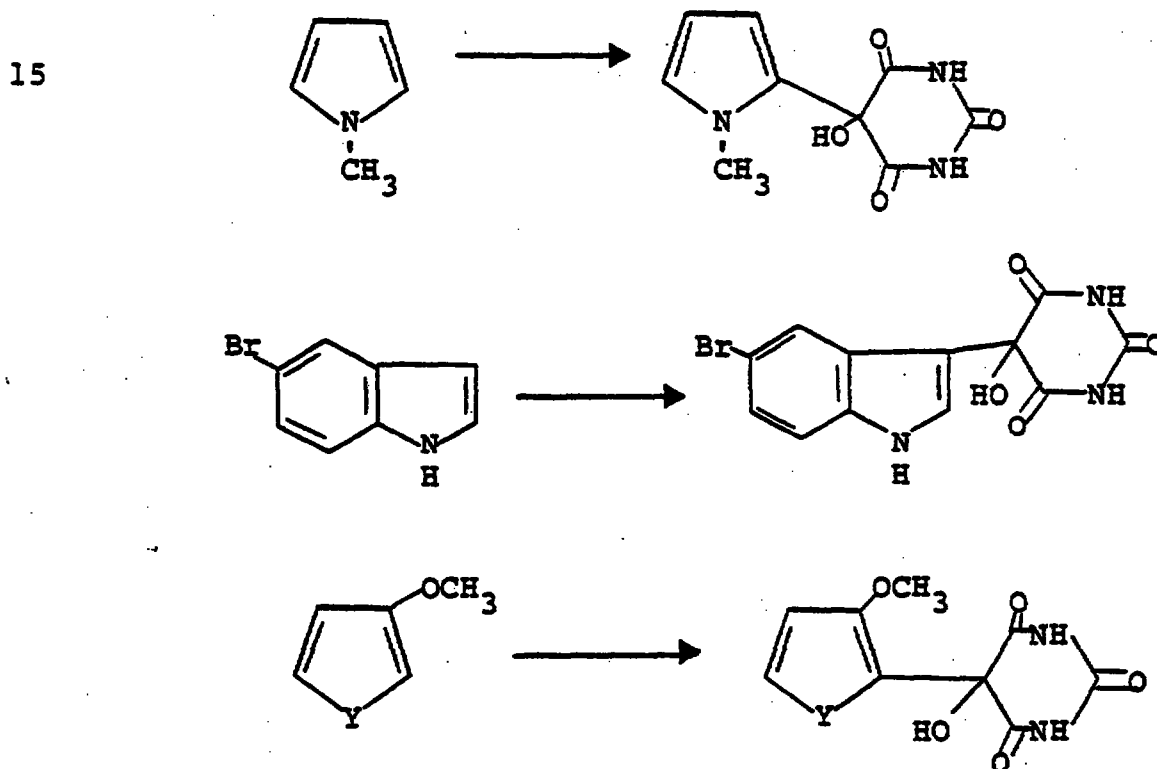
A general method for preparing dialuric acids appropriate as precursors of the oxazolidine-2,4-diones of the present invention is from the malonic ester derivatives (14), involving the two stages of base catalyzed condensation with urea and oxidation to the hydroxy or acyloxy compound. When the first stage is oxidation, the intermediate is a so-called tartronic acid derivative (15), while when the first stage is condensation, the intermediate is a so-called barbituric acid (16). When R^1 contains an amine function (e.g. 2-aminophenyl), it is preferred to carry out oxidation as the first stage, preventing possible complications of nitrogen oxidation. When condensation is the second stage, the dialuric acid is usually not isolated, at least in pure form, and is further converted, under basic conditions of the condensation, to the oxazolidine-2,4-dione.

Flowsheet II



The substituted malonic esters required for the above syntheses, when not available commercially, are obtained by literature methods, such as alcoholysis of alpha-cyano esters [cf. Steele, J. Am. Chem. Soc. 53, 286 (1931)], carbalkoxylation of esters [cf. Horning and Finelli, Org. Syntheses 30, 43 (1950)] and decarbonylation of alpha-keto esters obtained by the condensation of dialkyl oxalate with carboxylate esters [Reichstein and Morsman, Helv. Chim. Acta 17, 1123 (1934); Blicke and Zienty, J. Am. Chem. Soc. 63, 2946 (1941)].

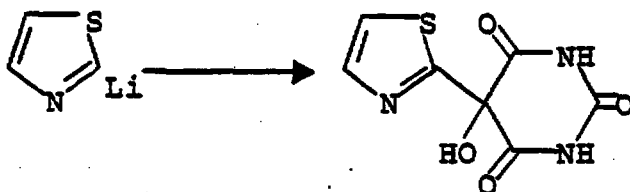
A less general method for the preparation of the appropriate dialuric acid intermediate is to react an electron rich heteroaryl/aryl compound, e.g.,



Now available is yet another method for the preparation of certain dialuric acid intermediates. This method, preferred when the appropriate starting materials are readily available, involves the reaction

20

of alloxan (preferably in anhydrous form) with the appropriate organometal derivative (e.g., organolithium, Grignard reagent). For example:



5 Protection strategies are required when using this method for preparation of certain oxazolidine-2,4-diones wherein R^1 carries a substituent which is not compatible with organometallic reactions, e.g., an acyl group is protected as its ethylenic ketal. In
10 other cases, such as when R^1 carries a group such as nitro or amino, this method generally lacks utility.

It will be evident to those skilled in the art that the preferred process for the oxazolidine-2,4-diones of the present invention will vary from one
15 given value of R^1 to another, depending upon such factors as availability of starting materials, yields, ability to remove undesirable impurities from the end-products, the chemical nature of the substituent groups contained in the final products, etc.

20 The pharmaceutically-acceptable cationic salts of the compounds of the present invention which form such salts are readily prepared by reacting the acid forms with an appropriate base, usually one equivalent, in a co-solvent. Typical bases are sodium hydroxide,
25 sodium methoxide, sodium ethoxide, sodium hydride, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, ethylenediamine, meglumine, benethamine, diethylamine, piperazine and tromethamine. Those salts
30 which do not precipitate directly are isolated by concentration to dryness or by addition of a

non-solvent. In some cases, salts can be prepared by mixing a solution of the acid with a solution of a different salt of the cation (sodium ethylhexanoate, magnesium oleate), employing a solvent in which the
5 desired cationic salt precipitates, or can be otherwise isolated by concentration and addition of a non-solvent.

The pharmaceutically acceptable acid addition salts of the compounds of the present invention which
10 form such salts are readily prepared by reacting the base forms with an appropriate acid, usually one equivalent, in a cosolvent. Typical acids are hydrochloric, hydrobromic, nitric, sulfuric, phosphoric, methanesulfonic, maleic, succinic, etc. Those salts
15 which do not precipitate directly are isolated by concentration to dryness or by addition of a non-solvent.

3-Acylated derivatives of the present invention are readily prepared by using standard conditions of
20 acylation, e.g. the reaction of the oxazolidine-2,4-dione salt (per se, or conveniently formed in situ by the addition of one equivalent of a tertiary amine such as triethylamine or N-methylmorpholine with an equivalent of the appropriate acid chloride or acid
25 anhydride) or reaction of the oxazolidine-2,4-dione with the appropriate organic isocyanate, optionally in the presence of a catalytic amount of tertiary amine base. In either case, the reaction is carried out in a reaction inert solvent, such as toluene,
30 tetrahydrofuran or methylene chloride. The temperature is not critical, and can be over a broad range (e.g. 0-150°C.). It will be evident to those skilled in the art that such acylation will be complicated by

competing or even selective sidechain (R^1) acylation when the sidechain contains a primary or secondary amine function.

5 It will be evident to those skilled in the art that the compounds of the present invention are asymmetric and therefore capable of existing in two optically active enantiomeric forms. The racemic compounds of the present invention, being acids when R is H, form salts with organic amines. These racemic forms
10 are therefore generally capable of resolution into the optically active forms by the classic method of forming diastereomeric salts with optically active amines, now separable by selective crystallization; alternatively those compounds containing a basic
15 amine function can be resolved by forming a salt with an optically active acid, preferably a strong organic acid such as a sulfonic acid. In general, one of the enantiomeric forms is found to have greater activity than the other.

20 The reactions employed to prepare the compounds of this invention can generally be monitored by standard tlc methods, employing commercially available plates. Suitable eluants are common solvents such as chloroform, ethyl acetate or hexane or suitable
25 combinations thereof which will differentiate starting materials, products, by-products, and in some cases intermediates. Applying these methods, which are well known in the art, will permit further improvement in the methodology of the specific examples detailed
30 hereinafter, e.g. the selection of more optimal reaction times and temperatures, as well as aid in the selection of optimal processes.

The oxazolidine-2,4-diones of the present invention are readily adapted to clinical use as anti-diabetic agents. The hypoglycemic activity required for this clinical use is defined by the glucose tolerance test procedure which follows. Intact male albino rats are the experimental test animals employed for such purposes. The test animals are fasted approximately 18-24 hours. The rats are weighed, numbered and recorded in groups of five or six as needed. Each group of animals is then dosed intraperitoneally with glucose (one gram per kilogram) and orally with either water (controls) or compound (at a level usually selected from the range 0.1 to 100 mg/kg). Blood glucose levels (mg/100 ml.) are measured in tail blood samples over a period of 3 hours in both control and treated groups. With equivalent zero hour blood glucose levels in control and treated groups, the % lowering of blood glucose at 0.5 hour, 1 hour, 2 hours and 3 hours is calculated as:

$$\frac{[\text{Control Blood Glucose}] - [\text{Treated Blood Glucose}]}{[\text{Control Blood Glucose}]} \times 100\%$$

Clinically useful hypoglycemic agents show activity in this test. The hypoglycemic activities determined for compounds of the present invention are summarized in Table I. This table records % blood glucose lowering at the 0.5 hour and 1 hour time points. A blood glucose lowering of 9% or greater generally reflects statistically significant hypoglycemic activity in this test. Those compounds which show significant activity only at the 2 hour or 3 hour points have such activity recorded in footnotes.

Table I
Hypoglycemic Activity of Oxazolidine-2,4-Diones
in the Rat Glucose Tolerance Test

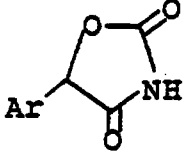
	Ar	Dose (mg./kg.)	% Lowering of Blood Glucose Level	
			0.5 hr.	1 hr.
5				
	2-Thienyl	10	11	8
	5-Benzoyl-	25	10	7
10	3-Bromo-	10	8	6(a)
	5-Bromo-	100	36	19
	5-Chloro-	100	26	17
	3-Methoxy-	5	13	16
	5-Methoxy-	25	9	7
15	3-Methyl-	100	30	17
		10	14	12
	5-Methyl	50	18	10
	5-Phenyl	50	1	5(b)
	3-Thienyl	10	23	20
20		5	20	17
	4-Bromo-	100	31	25
		10	14	9
	4-Methoxy-	5	11	8
	4-Methoxy-2-methyl-	5	16	14
25	4-Ethoxy-	5	19	19
	4-Ethoxy-2-methyl-	5	7	12
	4-Propoxy-	5	11	6
	2-Furyl	100	27	23
		10	11	7
30	3-Bromo-	25	18	10
		5	11	11
	5-Bromo-	50	19	20
		10	2	11

Table I. (Continued)

	<u>Ar</u>	<u>Dose</u> (mg./kg.)	<u>% Lowering</u> <u>of Blood Glucose Level</u>	
			<u>0.5 hr.</u>	<u>1 hr.</u>
5	5-Chloro-	25	21	20
	3-Methoxy-	25	10	10
	5-Methyl-	100	27	19
	5-Phenyl-	25	6	4(c)
	3-Furyl	10	17	13
10		5	14	8
	2,5-Dimethyl-	100	33(e)	16(f)
	4-Iodo-	25	19(e)	0(f)
	3-Benzo[b]thienyl	100	11	5
	7-Benzo[b]thienyl	100	-4	12(d)
15	7-Benzo[b]furanlyl	-	-	-
	5-Chloro-	10	23(e)	10(f)
	8-Chromanyl	-	-	-
	6-Chloro-	10	-	11
	6-Fluoro-	10	-	9
20	2,3-Dihydrobenzo- furanlyl	-	-	-
	5-Chloro-	25	-	23(g)
	2-Pyrrolyl	100	11	8
	1-Methyl-	100	18	17
	1-Ethyl-	100	14	16
25	1-(1-Butyl)-	100	4	13
	1-Phenyl	100	30	32
	3-Indolyl	-	-	-
	5-Bromo-	100	9	10
	1-Methyl-	100	11	8

Table I. (Continued)

	<u>Ar</u>	<u>Dose</u> (mg./kg.)	<u>% Lowering</u> <u>of Blood Glucose Level</u>	
			<u>0.5 hr.</u>	<u>1 hr.</u>
5	3-Pyridyl	-	-	-
	2-Methoxy	10	-	13
	2-Ethoxy-	25	-	20
	2-Methoxy-5-chloro-	25	22	17
	2-Ethoxy-5-chloro-	10	-	24(g)
10	5-Quinolyl	-	-	-
	6-Methoxy-	20	-	7(h)
	8-Quinolyl	18	19	16
	6-Chloro-	10	-	16
	6-Fluoro-	10	-	15
15	7-Methoxy-	10	-	-(i)
	2-Thiazolyl-	75	11	10
	2-Benzthiazolyl-	50	8	10
	5-isoxazolyl	-	-	-
	3-Methyl-	100	4	7(j)
20	(a) 11 at 2 hours.			
	(b) 9 at 2 hours.			
	(c) 10 at 3 hours.			
	(d) 16 at 2 hours; 10 at 3 hours.			
	(e) At 0.75 hours.			
25	(f) At 1.5 hours.			
	(g) At 0.75 hours.			
	(h) 9 at 2 hours.			
	(i) 12 at 3 hours.			
	(j) 24 at 2 hours, 14 at 3 hours.			

2
5 The oxazolidine-2,4-diones of the present invention are clinically administered to mammals, including man, via either the oral or the parenteral route. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired, as by disease or other abnormality, it is essential that the drug be administered parenterally. By either route, the dosage is in the range of about 0.10 to about 50 mg./kg. body weight of the subject per day, preferably about 0.20 to about 20 mg./kg. body weight per day administered singly or as a divided dose. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made to determine the most suitable dosage. This will vary according to the particular compound employed and with the subject being treated.

20 The compounds can be used in pharmaceutical preparations containing the compound, or pharmaceutically acceptable acid salt thereof, in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described above. Thus, for oral administration the compounds can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets,

powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions can if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral
5 administration the compounds can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions
10 of water-soluble pharmaceutically acceptable acid addition salts of the compounds. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously or intramuscularly, with intramuscular administration
15 being preferred in man.

The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the specific details of these examples.

EXAMPLE 1

Methyl 2-Methoxypyridine-3-carboxylate

Thionyl chloride (50 ml.) was added to 2-methoxy-
pyridine-3-carboxylic acid (5 g.) in 50 ml. of carbon
5 tetrachloride and the mixture refluxed for 2 hours.
The reaction mixture was cooled, evaporated to solids
and chased with multiple portions of fresh carbon
tetrachloride. The resulting acid chloride hydro-
chloride was dissolved in excess methanol (50 ml.),
10 stirred for 16 hours at room temperature, then evapo-
rated an oil and taken up in chloroform. The chloro-
form solution was washed with two portions of saturated
sodium bicarbonate and then one portion of brine,
dried over anhydrous magnesium sulfate, filtered and
15 evaporated to yield title product as an oil [4.63 g.;
pnmr/ CDCl_3/δ (ppm): 3.9 and 4.1 (2s, 6H), 6.9 (m,
1H), 8.2 (m, 2H)].

By the same procedure, 4-methylpyridine-3-carboxylic
acid is converted to methyl 4-methylpyridine-3-carboxy-
20 late.

EXAMPLE 2

3-Methanesulfinylmethylcarbonyl-2-Methoxypyridine

Sodium hydride (2.69 g., 50% dispersion in oil, 0.056 mole) was washed three times with petroleum ether. Following the third decantation, traces of petroleum ether were removed by evaporation in vacuo. Dimethylsulfoxide (30 ml.) was added and the mixture heated in an oil bath at 75°C. for 45 minutes, by which time hydrogen evolution had ceased. The mixture was cooled in an ice-water bath and diluted with 30 ml. of dry tetrahydrofuran. Title compound of the preceding Example (4.63 g., 0.028 mole) in 10 ml. of dry tetrahydrofuran was added dropwise over 5 minutes. The reaction mixture was warmed and stirred at room temperature for 30 minutes, poured into 180 ml. of water, acidified to pH 4 with 1N hydrochloric acid and extracted with three portions of chloroform. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to yield title product as an oil [4.97 g.; pnmr/ CDCl_3 / δ (ppm); 2.8 (s, 3H), 4.1 (s, 3H), 4.4 and 4.7 (2d, 2H), 7.0 (m, 1H), 8.3 (m, 2H)].

By the same procedure the 4-methyl compound of the preceding Example is converted to 3-methanesulfinylmethylcarbonyl-4-methylpyridine.

EXAMPLE 3

S-Methyl 2-Acetoxy-2-(2-methoxy-3-pyridyl)-
thioacetate

Title compound of the preceding Example (3.97 g.),
5 sodium acetate (3.97 g.) and acetic anhydride (40 ml.)
were combined in 80 ml. of toluene and heated at 115°
for 16 hours. The mixture was cooled and evaporated
to dryness in vacuo to yield crude product. The
latter was chromatographed on 200 g. of silica gel
10 with 2:1 chloroform:ethyl acetate as eluant, tlc
monitoring and collecting 10 ml. fractions. Clean
product fractions 58-79 were combined and concentrated
to an oil. To remove possible traces of residual
acetic anhydride, the oil was taken into wet ethanol,
15 held for 15 minutes, re-evaporated, chased with toluene,
taken up in chloroform, dried over anhydrous magnesium
sulfate, filtered, and re-evaporated to yield the
title product as an oil [3.16 g.; R_f 0.60 (3:1 ethyl
acetate: methanol); m/e 255; ir (CH₂Cl₂) 1748, 1686,
20 1582, 1460, 1205 cm⁻¹].

By the same procedure the methyl compound of the
preceding Example is converted to S-methyl 2-acetoxy-
2-(4-methyl-3-pyridyl)thioacetate.

EXAMPLE 4

5-(2-Methoxy-3-pyridyl)oxazolidine-2,4-dione

Sodium methoxide (632 mg., 11.7 mmoles) was taken into 50 ml. of absolute ethanol and the solution cooled in an ice-water bath. Urea (234 mg., 3.9 mmole) was added, followed by the title compound of the preceding Example (1.0 g., 3.9 mmole) in 5 ml. of ethanol. The mixture was heated at reflux for 16 hours, then cooled to room temperature, neutralized with 11.7 ml. of 1N hydrochloric acid and evaporated to a gum which was chased with toluene. The gum was chromatographed on 40 g. of silica gel with 1:2 ethyl acetate:chloroform as eluant, tlc monitoring and 10 ml. fractions collected. Product containing fractions 6-15 were combined and evaporated to a viscous oil, which was crystallized from water [75 mg; m.p. 183-186°C., Rf 0.32 (1:2 ethyl acetate:chloroform)].

By the same method, the methyl analog of the preceding Example is converted to 5-(4-methyl-3-pyridyl)oxazolidine-2,4-dione.

EXAMPLE 5

Ethyl 2-Ethoxypyridine-3-carboxylate

2-Ethoxypyridine-3-carboxylic acid (4 g.) was converted to its acid chloride hydrochloride by refluxing with 8.6 ml. of thionyl chloride for 60 minutes. The reaction mixture was evaporated to solids with toluene chase to removed the excess thionyl chloride. The residue was taken into 80 ml. of ethanol and held for 16 hours at 0°C., then evaporated to solids, which were partitioned between toluene and 1N sodium hydroxide. The aqueous layer was extracted with fresh toluene and the two organic layers combined, washed with water and then brine, dried over anhydrous magnesium sulfate, filtered and evaporated to yield title product as an oil [3.2 g.; pnmr/CDCl₃/delta (ppm) 1.6 (2s, 6H), 4.4-5.0 (2q, 4H), 7.2 and 8.2 (m, 3H)].

EXAMPLE 6

2-Ethoxy-3-methanesulfinylmethyl
carbonylpyridine

Using methylene chloride in place of chloroform
5 in the isolation, the procedure of Example 2 was
employed to convert product of the preceding Example
(3.0 g.) to title product [2.63 g.; m.p. 89-91°C.;
pnmr/ CDCl_3/δ (ppm), 1.5 (t, 3H), 2.8 (s, 3H), 4.2-
4.8 (s and q, 4H), 6.8-7.1 and 8.0-8.4 (3H)].

10 EXAMPLE 7

S-Methyl 2-Acetoxy-2-(2-ethoxy-3-pyridyl)-
thioacetate

Using a reaction time of 4 hours at 100°C. and
then 48 hours at room temperature, the procedure of
15 Example 3 was employed to convert the product of the
preceding Example (2.5 g.) to crude product, isolated
as an oil by evaporation of the reaction mixture. The
oil was taken up in ethyl acetate, washed in sequence
with three portions of 1N sodium hydroxide, one of
20 water and one of brine, dried over anhydrous magnesium
sulfate and evaporated to yield title product as an
oil [2.96 g.; Rf 0.78 (10:1 ethyl acetate:methanol);
m/e 269].

EXAMPLE 8

2-(2-Ethoxy-3-pyridyl)-2-hydroxyacetamide

Product of the preceding Example (2.9 g.) was
combined with 30 ml. of ethanol and 30 ml. of conc.
25 ammonium hydroxide, stirred at room temperature for 3
hours and then evaporated to yield crude product as an
oil (2.7 g.). The oil was chromatographed on 170 g.
of silica gel using ethyl acetate as eluant and tlc
monitoring. Clean product fractions were combined and
30 evaporated to yield title product as an oil [0.9 g.;
Rf 0.6 (10:1 ethyl acetate:methanol); pnmr/ CDCl_3/δ
(ppm) 1.4 (t, 3H), 4.5 (q, 2H), 5.4 (s, 1H), 6.2-8.2
(m, 5H)].

EXAMPLE 95-(2-Ethoxy-3-pyridyl)oxazolidine-2,4-dione

Product of the preceding Example (900 mg., 4.6 mmole) was combined with 25 ml. of tert-butanol.

5 Dimethyl carbonate (1.08 g., 9.2 mmole) and then potassium tert-butoxide (1.03 g., 9.2 mmole) were added and the reaction mixture refluxed for 3.5 hours. The reaction mixture was cooled, poured into 10 ml. of 1N hydrochloric acid, the pH adjusted to
10 7.0, and extracted with two portions of ethyl acetate. The aqueous layer was saturated with salt and extracted with additional ethyl acetate. The three organic layers were combined, back-washed with a small portion of water and then brine, dried over anhydrous magnesium
15 sulfate and evaporated to yield crude product as a viscous oil. Purified title product was obtained by crystallization from toluene (295 mg., m.p. 140-143°C.; m/e 272).

Anal. Calcd. for: $C_{10}H_{10}O_4N_2$:

20 C, 54.05; H, 4.54; N, 12.61.

Found: C, 54.34, H, 4.85, N, 12.70.

EXAMPLE 10Methyl 5-Chloro-2-methoxypyridine-3-
carboxylate

- By the procedure of Example 1, 5-chloro-2-methoxypyridine-3-carboxylic acid [Sarges et al., J. Med. Chem. 19, 709 (1976); 10 g.] was converted to its acid chloride, which was added in one portion to 150 ml. of methanol (slight exotherm), then made basic with triethylamine (approximately 1.1 equivalents).
- The reaction mixture was evaporated to solids and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was washed with fresh water and then brine, dried over anhydrous magnesium sulfate, filtered and evaporated to yield title product [9.75 g., m.p. 79-81°C.; $\text{pnmr}/\text{CDCl}_3/\delta$ (ppm) 3.8 (s, 3H), 4.1 (s, 3H), 8.1 (d, 1H), 8.3 (d, 1H)].

EXAMPLE 115-Chloro-3-methanesulfinylmethylcarbonyl-
2-methoxypyridine

- By the procedure of Example 2, the product of the preceding Example (9.7 g., 0.045 mole) was converted to title product isolated as a visous oil (10.3 g., m/e 249/247).

EXAMPLE 12S-Methyl 2-Acetoxy-2-(5-chloro-2-methoxy-3-pyridyl)thioacetate

Using a reaction time of 19 hours at 100°C., the procedure of Example 3 and the isolation method of Example 7 were employed to convert product of the preceding Example (10.3 g.) to title product in the form of a viscous oil (8.8 g.; pmr/CDCl_3 includes singlet at 6.4; m/e 291/289).

EXAMPLE 132-(5-Chloro-2-methoxy-3-pyridyl)-2-hydroxy-acetamide

Methanol (125 ml.) was saturated with anhydrous ammonia at 0-5°C. The product of the preceding Example (8.8 g.) in 25 ml. of methanol was added and the reaction mixture stirred overnight at room temperature, then concentrated to a viscous oil (7.3 g.). The oil was chromatographed on 400 g. of silica gel using 1:1 chloroform:ethyl acetate as eluant, tlc monitoring and 10 ml. fractions. Clean product fractions 190-270 were combined and evaporated to yield title product [1.3 g.; m.p. 110-113°C.; m/e 218/216; $\text{ir}(\text{KBr})$ 3444, 3410, 1684 cm^{-1}].

EXAMPLE 145-(5-Chloro-2-methoxy-3-pyridyl)oxazolidine-2,4-dione

Using a reflux period of 15 hours, the procedure of Example 9 was employed to convert the product of the preceding Example (1.25 g., 5.8 mmoles) to title product. To isolate, the reaction mixture was cooled to room temperature and the pH adjusted to 3 with 1N hydrochloric acid. The mixture was then evaporated in vacuo to slightly gummy solids, which gave filterable, crude product on stirring with 25 ml. of water (1.09 g., m.p. 199-204°C. Recrystallization from 15 ml. of ethanol gave purified title product [470 mg.; m.p. 212-214°C.; m/e 244/242; $\text{ir}(\text{KBr})$ 3174, 3074, 2980, 1830, 1752 cm^{-1}].

EXAMPLE 152-(6-Chloro-8-quinolyl)-2-hydroxyacetamide

Ethyl 2-(6-chloro-8-quinolyl)-2-hydroxyacetate (1.6 g.) in 300 ml. of conc. ammonium hydroxide was heated to reflux. Since complete dissolution did not result, the reaction mixture was cooled, diluted with 50 ml. of ethanol and reheated to reflux for 0.5 hour. The reaction mixture was concentrated to a volume of 100 ml., cooled slowly and a crop of title product (320 mg., m.p. 195-198°C.) recovered by filtration. Additional product (145 mg.) was recovered by concentration of the mother liquor to 50 ml. and extraction into three portions of ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness.

By the same procedure, ethyl 2-(6-chloro-2,3-dihydro-7-benzo[b]furanyl)-2-hydroxyacetate is converted to ethyl 2-(6-chloro-2,3-dihydro-7-benzo[b]furanyl)-2-hydroxyacetamide.

EXAMPLE 165-(6-Chloro-8-quinolyl)oxazolidine-2,4-dione

Potassium tert-butoxide (292 mg., 2.6 mmoles) was dissolved in 20 ml. of tert-butanol. Dimethyl carbonate (234 mg. 2.6 mmoles) and then title compound of the preceding Example (300 mg., 1.3 mmoles) were added. The reaction mixture refluxed for 18 hours, then cooled to room temperature, adjusted to pH 3 with 1N hydrochloric acid and diluted with 1N hydrochloric acid and ethyl acetate. The aqueous layer was washed with two additional portions of ethyl acetate. The organic layers were combined, washed with two portions of fresh 1N hydrochloric acid and then brine, dried over anhydrous magnesium sulfate, filtered and evaporated to an oil (130 mg.). Crystallization of the oil from isopropyl ether gave purified title product [58 mg., m.p. 207-210°C.; ir(KBr) 1839, 1825, 1740 cm^{-1}].

By the same procedure the benzofuran analog of the preceding Example is converted to 5-(6-chloro-2,3-dihydro-7-benzo[b]furanyl)oxazolidine-2,4-dione.

EXAMPLE 172-(6-Fluoro-8-quinolyl)-2-hydroxyacetamide

5 Ethyl 2-(6-fluoro-8-quinolyl)-2-hydroxyacetate (1.1 g.) was refluxed for 10 minutes in 300 ml. of conc. ammonium hydroxide. The reaction mixture was cooled slightly, clarified by filtration and evaporated to solids. Trituration of the residue with 25 ml. of toluene gave the title product (860 mg., m.p. 169-171°C.).

EXAMPLE 185-(6-Fluoro-8-quinolyl)oxazolidine-2,4-dione

10 Using a reflux period of 3.5 hours, the product of the preceding Example (840 mg., 3.8 mmoles) was converted to title product by the procedure of Example 15 16. In this case, a pH of 2 was used in the isolation without addition of excess 1N hydrochloric acid and the crude product was recrystallized from toluene [120 mg., m.p. 202-204°C.; m/e 246; ir(KBr) 1819, 1743, 1363 cm^{-1}].

EXAMPLE 195-(8-Quinolyl)oxazolidin-4-one-2-thione

Potassium thiocyanate (484 mg., 4.9 mmoles) and potassium cyanide (370 mg., 5.7 mmoles) were combined in 5 ml. of water and cooled to 0°C. Quinoline-8-carbaldehyde [J. Org. Chem. 41, p. 957 (1976); 779 mg., 4.9 mmoles] was added, followed by the dropwise addition of hydrochloric acid (30%, 1.9 ml.). After stirring for 25 minutes at 0°C., the reaction mixture was heated to 90-100°C. for 25 minutes, cooled, quenched into crushed ice, adjusted to pH 8 with sodium bicarbonate and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness (163 mg.). The latter was partitioned between 1N sodium hydroxide and ethyl acetate. The basic layer was acidified and extracted with fresh ethyl acetate. The two ethyl acetate layers were combined, dried, filtered and evaporated to yield title product [72 mg.; Rf 0.65 (ethyl acetate)]. The original, pH 8 aqueous layer was salted and extracted with ethyl acetate to yield an additional crop (114 mg.). The last aqueous phase was acidified and extracted with ethyl acetate to yield a third crop (115 mg.).

By the same method, 7-chloroquinoline-8-carbaldehyde is converted to 5-(7-chloro-8-quinolyl)oxazolidin-4-one-2-thione.

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EXAMPLE 20

5-(8-Quinolyl)oxazolidine-2,4-dione

Title compound of the preceding Example (230 mg., 0.94 mmole) was taken into 6 ml. of 2:1 methanol:water and cooled to 0°C. Bromine (0.07 ml., 21.7 mg., 2.7 mmoles) was added and the reaction mixture allowed to warm slowly to room temperature, then stirred for 1 hour. The reaction mixture was evaporated to dryness and the residue partitioned between 1N sodium hydroxide and ethyl acetate. The aqueous layer was separated, acidified and extracted with two portions of fresh ethyl acetate. The acidic extracts were combined, dried and evaporated to an oil (144 mg.). Crystallization from toluene-chloroform and recrystallization from toluene gave purified title product (40 mg., m/e 228).

Anal. Calcd. for: $C_{12}H_8O_3N_2 \cdot 0.33H_2O$:

C, 61.54; H, 3.70; N, 11.96.

Found:

C, 61.50; H, 3.89; N, 11.52.

By the same method the chloro compound of the preceding Example is converted to 5-(7-chloro-8-quinolyl)-oxazolidine-2,4-dione.

EXAMPLE 21

5-(6-Methoxy-5-quinolyl)oxazolidin-4-one-2-thione

By the procedure of Example 19, 6-methoxyquinoline-5-carbaldehyde (0.77 g.) was converted to title product. After quenching into ice, a first crop (190 mg.) was isolated by extraction into ethyl acetate, drying over anhydrous magnesium sulfate and evaporation to dryness. A second crop (176 mg.) was isolated in like manner by adjusting the aqueous phase to pH 8 with bicarbonate and extracting with additional ethyl acetate. Both crops had m/e 274. The second crop also had m/e 258, indicating contamination with the product of the next step.

EXAMPLE 225-(6-Methoxy-5-quinolyl)oxazolidine-2,4-dione

The combined product crops of the preceding Example (0.36 g., 1.31 mmole) were taken into 15 ml. of methanol. Sodium metaperiodate (0.56 g., 2.62 mmols) in 7.2 ml. of 5% sodium bicarbonate was added dropwise. After stirring for 3 hours at room temperature, the reaction mixture was quenched with water, acidified and extracted with two portions of ethyl acetate. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness (110 mg.). The aqueous phase was adjusted to pH 7 and further crude product (100 mg.) obtained by extraction with ethyl acetate. The crude crops were combined, taken into 1N sodium hydroxide, acidified to pH 4 with acetic acid and extracted with fresh ethyl acetate. The latter organic extracts were combined and evaporated to dryness. Trituration of the residue with ether, allowing the mixture to stand until crystallization was complete, gave title product (34 mg.; m.p. 144-146°C.).

EXAMPLE 235-(7-Methoxy-8-quinolyl)oxazolidin-4-one-2-thione

By the procedure of Example 19, but using adjustment to pH 7 with bicarbonate after quench and ethyl acetate for extraction, 7-methoxyquinoline-8-carbaldehyde (2.0 g., 10.7 mmoles) was converted to title product [1.17 g.; Rf 0.7 (2:1 ethyl acetate:chloroform)]. This product was not partitioned between aqueous base and ethyl acetate, nor was a second crop isolated by salting the aqueous phase and further extracting.

EXAMPLE 245-(7-Methoxy-8-quinolyl)oxazolidine-2,4-dione

Product of the preceding Example (0.74 g., 2.7 mmoles) was combined with 30 ml. of methanol and 15 ml. of 5% sodium bicarbonate. Sodium metaperiodate (1.15 g., 5.4 mmoles) in 15 ml. of water was added dropwise. After stirring for 3 hours at room temperature, the reaction mixture was quenched with water, acidified to pH 2-3 and extracted with two portions of ethyl acetate. The extracts were combined, dried and evaporated to dryness (360 mg.). Recrystallization from water gave purified title product (100 mg.; m.p. 207-208°C.).

Anal. Calcd. for $C_{13}H_9N_2O_3 \cdot 1.2H_2O$:

C, 59.40; H, 4.34; N, 10.66.

Found:

C, 59.33; H, 4.01; N, 10.66.

EXAMPLE 255-Hydroxy-5-(1-methyl-2-pyrrolyl)-2,4,6-
(1H,3H,5H)pyrimidinetrione

Alloxan hydrate (3.2 g., 0.02 mole) was dissolved
5 in 50 ml. of ethanol by warming. 1-Methylpyrrole
(1.6 g., 0.02 mole) was added and the mixture warmed
for 5 minutes on a steam bath, while perfusing with
hydrogen chloride. After standing at room temperature
10 for 0.5 hour, the reaction mixture was evaporated to
dryness and the residue triturated with water to yield
title product as a solid [2.9 g.; m/e 223; Rf 0.5 (1:1
ethyl acetate:hexane/5% acetic acid)].

EXAMPLE 265-(1-Methyl-2-pyrrolyl)oxazolidine-2,4-dione

15 Product of the preceding Example (2.8 g.) was
combined with 25 ml. of 1N sodium hydroxide and heated
on a steam bath for 30 minutes, by which time complete
dissolution had occurred. On acidification, a gum
precipitated, which solidified on trituration with
20 water (1.2 g.). Recrystallization from methanol-ether
afforded purified title product [0.70 g.; m.p. 108-114
(dec); m/e 180].

Anal. Calcd. for $C_8H_8O_3N_2$: C, 53.33; H, 4.48; N, 15.55.
Found: C, 53.16; H, 4.72; N, 15.28.

EXAMPLE 275-Hydroxy-5-(1-ethyl-2-pyrrolyl)-2,4,6-
(1H,3H,5H)pyrimidinetrione

Potassium pyrrole [J. Chem. Soc., p. 52 (1931);
25 1 g.; 0.01 mole] was slurried in 5 ml. of tetrahydro-
furan. Ethyl iodide (1 ml., 0.012 mole) was added, a
slight exotherm being noted. The mixture was stirred
for 0.5 hour, heated to reflux for 0.5 hour, cooled to
room temperature, diluted with 15 ml. of water and
30 extracted with 10 ml. of ether. The ether extract was
washed with 5 ml. of water, then added to alloxan
hydrate (1.6 g.) which had been dissolved in 25 ml. of
ethanol by heating. The ether was boiled off and the
ethanolic residue refluxed for 0.5 hour, then evapo-
35 rated to a water-soluble gum. The gum was taken up in
25 ml. of ethyl acetate, washed with two 10 ml. portions
of water and re-evaporated to yield title product as a
gum (0.6 g., m/e 237).

EXAMPLE 285-(1-Ethyl-2-pyrrolyl)oxazolidine-2,4-dione

The procedure of the preceding Example was repeated on a three times scale. The initially isolated product gum (0.03 mole of the pyrimidinetrione) was stirred with 60 ml. of 1N sodium hydroxide for 0.5 hour, then acidified with conc. hydrochloric acid and extracted with ethyl acetate. The extract was filtered from insoluble impurities, and concentrated to a gum (2.2 g.). The gum was chromatographed on 100 ml. of silica gel with (1:1 ethyl acetate:hexane as eluant and tlc monitoring. Early fractions contained the desired product; these were combined and evaporated to an oil which crystallized on standing. Trituration with water gave purified title product (170 mg.; m.p. 90-93°C.; m/e 194).

Anal. Calcd. for $C_9H_{10}O_3N_2 \cdot 0.25H_2O$:

C, 54.40; H, 5.32; N, 14.10.

Found:

C, 54.37; H, 5.16; N, 13.76.

EXAMPLE 295-Hydroxy-5-[1-(1-butyl)-2-pyrrolyl]-
2,4,6-(1H,3H,5H)pyrimidinetrione

Potassium pyrrole (3.0 g., 0.03 mole), 1-iodobutane (9.2 g., 0.05 moles) and 10 ml. of tetrahydrofuran were combined and refluxed for 1.5 hours by which time the reaction mixture had become a thick mass. The reaction mixture was diluted with 30 ml. of water and extracted with 35 ml. of ether. The ether was back-washed with water, then added to a solution of anhydrous alloxan (4.8 g., 0.03 mole) obtained by heating in 50 ml. of ethanol. The ether was distilled away, 6N hydrochloric acid (5 ml., 0.03 mole) was added, and the mixture refluxed for 3 minutes, cooled, evaporated to a gum, and triturated with water to afford title product [5.1 g.; m.p. 135 (dec); m/e 265].

EXAMPLE 30

5-[1-(1-Butyl)-2-furyl]oxazolidine-2,4-dione

Product of the preceding Example (5.1 g., 0.019 mole) was combined with 1N sodium hydroxide (38 ml., 0.038 mole) and stirred at room temperature for 10 minutes. The reaction mixture was filtered, washed with ether, cooled in an ice-water bath, acidified with conc. hydrochloric acid and extracted with three portions of ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate and evaporated to gummy solids. The latter was chromatographed on silica gel with ethyl acetate as eluant and tlc monitoring to yield partially purified product isolated as an oil (950 mg.). The latter was rechromatographed using 1:1 ethyl acetate:hexane as eluant, yielding purified title product as an oil [0.59 g.; m/e 222; Rf 0.72 (ethyl acetate)].

Anal. Calcd. for $C_{11}H_{14}O_3N_2 \cdot 0.5H_2O$:

	C, 57.38; H, 6.57; N, 12.17.
Found:	C, 57.40; H, 6.35; N, 12.15.

EXAMPLE 31

Sodium 5-[1-(1-butyl)-2-furyl]oxazolidine-2,4-dione

Product of the preceding Example (370 mg., 1.66 mmoles) was dissolved in 5 ml. of methanol. Sodium bicarbonate (90 mg., 1.66 mmoles) was added. The resulting solution was evaporated to dryness and the solid residue triturated with ether to yield the title product [300 mg.; m.p. 123-126°C. (dec); tlc mobility with 1:1 ethyl acetate:hexane/5% acetic acid as eluant identical with the free base form].

EXAMPLE 32

5-Hydroxy-5-(1-phenyl-2-pyrrolyl)-2,4,6-
(1H,3H,5H)pyrimidinetrione

1-Phenylpyrrole (1.4 g., 0.01 mole), alloxan
hydrate (1.6 g., 0.01 mole) and 50 ml. of ethanol were
combined and refluxed for 15 minutes. No reaction was
noted by tlc. 1N Hydrochloric acid (10 ml., 0.01
mole) was added and the acidified mixture refluxed for
15 minutes. Incomplete reaction was noted by tlc. A
second portion of alloxan hydrate (1.6 g., 0.01 mole)
was added and the mixture refluxed another 15 minutes,
cooled and evaporated to dryness. Trituration of the
residue with water gave title product [2.3 g.; m/e
285; m.p. 232-234°C. (dec); Rf 0.3 (1:1 ethyl acetate:
hexane)].

Anal. Calcd. for $C_{14}H_{11}O_4N_3 \cdot 0.25H_2O$:

C, 58.01; H, 4.00; N, 14.50.

Found:

C, 57.84; H, 4.05; N, 14.56.

EXAMPLE 33

5-(1-Phenyl-2-pyrrolyl)oxazolidine-2,4-dione

The product of the preceding Example (1 g.) was
heated on a steam bath for 20 minutes with 20 ml. of
1N sodium hydroxide. The mixture was then cooled in
an ice-water bath, acidified with conc. hydrochloric
acid and the supernatant decanted from the resulting
gummy precipitate. The gum was taken up in ethyl
acetate, washed with water, and evaporated to an oil
(0.47 g.). The aqueous decant was also extracted with
ethyl acetate, the extract back washed with water and
evaporated to a second oil (0.28 g.). The two oils
were combined, chromatographed on 150 ml. of silica
gel with 1:1 ethyl acetate:hexane as eluant and tlc
monitoring. The early, product fractions were combined,
evaporated to an oil (410 mg.) and the oil crystallized
from ether-hexane to yield purified title product
[280 mg.; m.p. 130-132°C.; m/e 242; Rf 0.47 (1:1 ethyl
acetate:hexane)].

Anal. Calcd. for $C_{13}H_{10}O_3N_2$: C, 64.46; H, 4.16; N, 11.57.

Found:

C, 64.40; H, 4.35; N, 11.56.

EXAMPLE 345-Hydroxy-5-(1-methyl-3-indolyl)-2,4,6,-
1H,3H,5H)pyrimidinetrione

Alloxan hydrate (1.6 g., 0.01 mole) 1-methylindole
5 (1.3 g., 0.01 mole) and ethanol (50 ml.) were combined
and the mixture refluxed for 0.5 hour, then concen-
trated to half-volume, diluted with water and the
resulting product recovered by filtration [2.7 g., Rf
0.5 (1:1 ethyl acetate:hexane/5% acetic acid)].

10

EXAMPLE 355-(1-Methyl-3-indolyl)oxazolidine-2,4-dione

Product of the preceding Example (2 g.) was
heated on a steam bath for 15 minutes with 35 ml. of
1N sodium hydroxide. The reaction mixture was cooled
15 to room temperature, acidified to pH 1 with conc.
hydrochloric acid, and decanted from a small amount of
gum (130 mg.). The decant was clarified by filtration,
cooled in an ice-water bath, and the resulting solids
(330 mg.) recovered by filtration. The filtrate was
20 extracted with ethyl acetate; the extract was back-
washed with water and evaporated to solids (0.61 g.).
The solid products were combined and recrystallized
from ethyl acetate/hexane to yield title product
(0.33 g.; m.p. 152-153.5°C.).

25

Anal. Calcd. for $C_{12}H_{10}O_3N_2 \cdot 0.125H_2O$:

C, 61.99; H, 4.45; N, 12.05.

Found:

C, 61.99; H, 4.45; N, 12.02.

58

49

EXAMPLE 36

5-Hydroxy-5-(5-bromo-3-indolyl)-2,4,6-
(1H,3H,5H)pyrimidinetrione

5 Alloxan hydrate (1.6 g., 0.01 mole) was dissolved
in 40 ml. of ethanol by heating. 5-Bromoindole (1.96 g.,
0.01 mole) was added and heating near reflux continued
for 15 minutes. Tlc did not indicate that reaction
had occurred. 1N Hydrochloric acid (10 ml.) was then
added while maintaining the reaction near reflux.
10 After 10 minutes, the reaction was concentrated to wet
solids. Trituration of these wet solids with water
gave the title product [3.17 g., m.p. 250°C.; Rf 0.45
(1:1 ethyl acetate:hexane/5% acetic acid); Rf 0.3 (1:5
ethyl acetate:hexane/5% acetic acid)].

15

EXAMPLE 37

5-(5-Bromo-3-indolyl)oxazolidine-2,4-dione

Product of the preceding Example (3.1 g.) was
heated on a steam bath with 50 ml. of 1N sodium hy-
droxide for 15 minutes, then cooled and crude product
20 (1.25 g.) precipitated by acidification with conc.
hydrochloric acid. Chromatography on silica gel,
using 1:1 ethyl acetate:hexane as eluant and tlc
monitoring gave purified title product [0.41 g.; m.p.
185-189°C.; Rf 0.55 (1:5 ethyl acetate:hexane/5%
25 acetic acid)].
Anal. Calcd. for $C_{11}H_7O_3N_2Br$: C, 44.76; H, 2.38; N, 9.49.
Found: C, 45.10; H, 2.68; N, 9.58.

EXAMPLE 38

5-Hydroxy-5-(2-thiazolyl)-2,4,6-
(1H,3H,5H)pyrimidinetrione

Thiazole (1.7 g., 0.02 mole) was dissolved in
5 tetrahydrofuran (35 ml.) and cooled to -60°C. Butyl-
lithium (9 ml. of 2.4M in hexane, 0.0216 mole) was
added dropwise over 20 minutes, and the reaction mix-
ture stirred for an additional 30 minutes at -60°C.
In this manner 2-thiazolyl lithium was formed. Anhydrous
10 alloxan (3 g., 0.021 mole) was dissolved in 20 ml. of
tetrahydrofuran and added dropwise over 20 minutes,
keeping the temperature at -60°C. The stirred reaction
mixture was warmed to room temperature over 30 minutes,
then recooled to 0°C. 1N Hydrochloric acid (25 ml.)
15 was added portion wise and the quenched reaction
mixture extracted with 50 ml. of ethyl acetate. The
ethyl acetate extract was back-washed with 15 ml. of
water, dried over anhydrous sodium sulfate, filtered
and evaporated to yield title product [1.9 g.; m/e
20 227; Rf 0.4 (1:1 ethyl acetate:hexane/5% acetic acid)].

By the same procedure, oxazole is converted to 5-
hydroxy-5-(2-oxazolyl)-2,4,6-(1H,3H,5H)pyrimidinetrione.

EXAMPLE 39

5-(2-Thiazolyl)oxazolidine-2,4-dione

Title product of the preceding Example (1.37 g.)
was stirred at room temperature with 24 ml. of 1N
25 sodium hydroxide. The reaction mixture was allowed to
stand for 25 minutes, acidified with 3 ml. of glacial
acetic acid and extracted with two 50 ml. portions of
ethyl acetate. The extracts were separately dried
over sodium sulfate, filtered and evaporated to solids,
30 the first yielding 184 mg., the second 85 mg. These
solids were combined and chromatographed on 50 ml. of
silica gel with 1:1 ethyl acetate:hexane/5% acetic
acid as eluant and tlc monitoring. Clean product
fractions were combined, evaporated to dryness and the
35 residue triturated with hexane to yield purified title
product (155 mg.; m.p. 150-152°C.).

Anal. Calcd. for C ₆ H ₄ O ₃ N ₂ S:	C, 39.13; H, 2.19; N, 15.21.
Found:	C, 39.53; H, 2.52; N, 14.95.

By the same procedure, the other product of the
40 preceding Example is converted to 5-(2-oxazolyl)oxa-

EXAMPLE 405-Hydroxy-5-(2-benzthiazolyl)-2,4,6-
(1H,3H,5H)pyrimidinetrione

By the procedure of Example 38, benzthiazole
(2.7 g., 0.02 moles) was converted to its 2-lithio
derivative and then reacted with anhydrous alloxan to
yield title product, initially isolated as an oil.
The latter was crystallized from ether-hexane [2.2 g.;
Rf 0.55 (1:1 ethyl acetate:hexane/5% acetic acid)].

EXAMPLE 415-(2-Benzthiazolyl)oxazolidine-2,4-dione

Product of the preceding Example (2.15 g.) was
stirred with 30 ml. of 1N sodium hydroxide for 30
minutes. The reaction mixture was extracted with
ether and product (0.46 g.) precipitated by acidifi-
cation of the aqueous layer with 6N hydrochloric acid.
Chromatography on 50 ml. of silica gel with 1:1 ethyl
acetate:hexane/5% acetic acid as eluant and tlc
monitoring, followed by recrystallization from acetone-
isopropyl ether gave purified title product [110 mg.,
m.p. 214-216°C. (dec)].

Anal. Calcd. for $C_{10}H_6O_3N_2S$: C, 51.29; H, 2.58; N, 11.96.
Found: C, 51.51; H, 2.99; N, 12.21.

EXAMPLE 422-(6-Chloro-8-chromanyl)-2-trimethylsiloxy-ethanenitrile

5 6-Chlorochroman-8-carbaldehyde (7 g., 0.036 mole)
in 70 ml. of methylene chloride was cooled to 0-5°C.
Zinc iodide (100 mg.) was added, followed by the drop-
wise addition of trimethylsilylcarbonitrile (4.26 g.,
0.043 mole). The reaction mixture was stirred at room
10 temperature for 64 hours, then washed in sequence with
three portions of saturated sodium bicarbonate and one
of brine, dried over anhydrous magnesium sulfate,
filtered and evaporated to yield title product as an
oil [9.5 g.; $\text{ir}(\text{CH}_2\text{Cl}_2)$ 2857, 1479, 1215, 1190, 1060
 cm^{-1}].

15

EXAMPLE 43Ethyl 1-(6-Chloro-8-chromanyl)-1-hydroxy-methanecarboximidate Hydrochloride

To cold (0-5°C.), saturated ethanolic hydrogen
chloride (250 ml.) there was added, in a dropwise
20 manner, product of the preceding Example (9.29 g.) in
15 ml. of ethanol, keeping the temperature below 10°C.
The mixture was stirred at 0-5°C. for 35 minutes and
then evaporated to an oil. Crystallization from
ethanol-ether gave title product [5.7 g.; m.p. 125-
25 127° (dec); m/e 271/269].

EXAMPLE 445-(6-Chloro-8-chroman-2-yl)oxazolidine-2,4-dione

Product of the preceding Example (5.4 g., 18.6 mmols) was suspended in 250 ml. of tetrahydrofuran, cooled in an ice-water bath, and triethylamine (6.01 g., 0.06 mole) added. The cold mixture was perfused with phosgene for 30 minutes, stirred at room temperature for 1 hour and then poured into 1 liter of crushed ice. The quenched reaction mixture was extracted with three portions of methylene chloride. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated to solids. The residue was recrystallized from toluene to yield purified title product (3.28 g., m.p. 170-172°C., m/e 269/267).

Anal. Calcd. for $C_{12}H_{10}O_4NCl$: C, 53.84; H, 3.77; N, 5.23.

Found: C, 53.73; H, 3.83; N, 5.48.

EXAMPLE 452-(6-Fluoro-8-chroman-2-yl)-2-trimethylsiloxy-ethanenitrile

By the procedure of Example 42, 6-fluorochroman-8-carbaldehyde (3.2 g., 0.0178 mole) was converted to title product as an oil [4.51 g., m/e 279; ir ($CHCl_2$) 1498, 1205, 1066 cm^{-1}].

EXAMPLE 46Ethyl 1-(6-Fluoro-8-chroman-1-yl)-1-hydroxy-methanecarboximidate Hydrochloride

5 Using a reaction time of 1 hour at 0-5°C., the procedure of Example 43 was employed to convert product of the preceding Example (4.4 g.) to title product [4.1 g.; m.p. 124-126°C. (dec); m/e 253].

EXAMPLE 475-(6-Fluoro-8-chroman-1-yl)oxazolidine-2,4-dione

10 By the procedure of Example 44, product of the preceding Example (3.9 g., 0.0134 mole) was converted to crude title product. Crude solids were taken into 1N sodium hydroxide and extracted with two portions of ether. Product was reprecipitated by adding the basic
15 aqueous layer slowly to excess 3N hydrochloric acid. Recrystallization from toluene gave purified title product [2.73 g.; m.p. 174-176°C.; m/e 251].
Anal. Calcd. for $C_{12}H_{10}O_4NF$: C, 57.37; H, 4.01; N, 5.58.
Found: C, 57.74; H, 3.91; N, 5.40.

EXAMPLE 482-(5-Chloro-2,3-dihydro-7-benzo[b]furan-1-yl)-2-trimethylsiloxyethanenitrile

25 5-Chloro-2,3-dihydrobenzo[b]furan-7-carbaldehyde (900 mg., 4.9 mmoles) was dissolved in 25 ml. of ether. Zinc iodide (20 mg.) and then trimethylsilyl-carbonitrile (970 mg., 9.8 mmoles) were added and the mixture stirred 16 hours at room temperature, then
30 diluted with 50 ml. ether, washed with three portions of saturated sodium bicarbonate and one of brine, dried over anhydrous magnesium sulfate, filtered and evaporated to yield title product as an oil [1.4 g.; m/e 283/281; $\nu(\text{CHCl}_2)$ 1479, 1457, 1435, 1180, 866, 848 cm^{-1}].

35 By the same method 5-fluoro-2,3-dihydrobenzo[b]furan-7-carbaldehyde is converted to 2-(5-fluoro-2,3-dihydro-7-benzo[b]furan-1-yl)-2-trimethylsiloxyethanenitrile.

EXAMPLE 49

Ethyl 1-(5-Chloro-2,3-dihydro-7-benzo[b]-
furanyl)-1-hydroxymethanecarboximidate

Hydrochloride

5 By the procedure of Example 43, title compound of
the preceding Example (1.37 g.) was converted to title
product. The initially isolated solids were repulped
twice in ether to obtain purified product [1.28 g.;
m.p. 149-152°C. (dec); m/e 257/255; ir(KBr) 3162,
10 2875, 1650, 1524, 1458 cm⁻¹].

By the same method the fluoro compound of the
preceding Example is converted to ethyl 1-(5-fluoro-
2,3-dihydro-7-benzo[b]furanyl)-1-hydroxymethanecarbox-
imidate hydrochloride.

EXAMPLE 50

5-(5-Chloro-2,3-dihydro-7-benzo[b]furanyl)-
oxazolidine-2,4-dione

15 By the procedure of Example 44, title compound of
the preceding Example (1.1 g.) was converted to toluene
recrystallized title product [630 mg.; m.p. 197-
20 199°C.; m/e 255/253; ir(KBr) 3084, 1833, 1810, 1746
cm⁻¹].

By the same procedure the fluoro analog of the
preceding Example is converted to 5-(5-fluoro-2,3-
25 dihydro-7-benzo[b]furanyl)oxazolidine-2,4-dione.

EXAMPLE 51

2-(3-Methyl-5-isoxazolyl)-2-trimethylsilyl-ethanenitrile

5 By the procedure of Example 42, 3-methylisoxazole-5-carbaldehyde (3.4 g., 0.032 mole) was converted to title product, isolated as an oil (6.5 g., no aldehyde proton by nmr).

10 By the same method, isothiazole-5-carbaldehyde is converted to 2-(5-thiazolyl)-2-trimethylsilylethanenitrile and 5-methylisoxazole-3-carbaldehyde (Kane et al., Japan 62/17,572) is converted to 2-(5-methyl-3-isoxazolyl)-2-trimethylsilylethanenitrile.

EXAMPLE 52

15 Ethyl 1-Hydroxy-1-(3-methyl-5-isoxazolyl)-methanecarboximate Hydrochloride

Title product of the preceding Example (6.5 g.) was dissolved in cold, saturated ethanolic hydrogen chloride (50 ml.) and held at 5°C. for 16 hours. Title product was recovered by filtration (3.3 g., 20 m.p. 119-121°C.).

25 By the same method, the other products of the preceding Example are converted to ethyl 1-hydroxy-1-(5-isothiazolyl)methanecarboximate hydrochloride and ethyl 1-hydroxy-1-(5-methyl-3-isoxazolyl)methanecarboximate hydrochloride.

EXAMPLE 535-(3-Methyl-5-isoxazolyl)oxazolidine-2,4-dione

By the procedure of Example 44, title product of the preceding Example (2.2 g.), was converted to title product. After quench into crushed ice, the product was extracted into ether, the combined extracts dried and evaporated to an oil (1.4 g.). Further extraction with ethyl acetate and evaporation gave additional oil (0.4 g.). The oils were combined and partitioned between 25 ml. of 1N sodium hydroxide and 25 ml. of ether. The basic aqueous phase was separated, acidified with conc. hydrochloric acid and extracted with 25 ml. of ethyl acetate. The ethyl acetate extract was back-washed with water, evaporated to dryness, the residue triturated with ether (146 mg., m.p. 173-175°C.). The ether triturate was evaporated to dryness and triturated with fresh ether (238 mg., m.p. 175-177°C.).

By the same method, the other products of the preceding Example are converted to 5-(5-isothiazolyl)-oxazolidine-2,4-dione and 5-(5-methyl-3-isoxazolyl)-oxazolidine-2,4-dione.

EXAMPLE 545-(5-Chloro-2-ethoxy-3-pyridyl)oxazolidine-2,4-dione

5-(2-Ethoxy-3-pyridyl)oxazolidine-2,4-dione (125 mg.) was suspended in 100 ml. of water and dissolved by warming to 56°C. Chlorine was bubbled into the warm solution for 30 minutes, during which time the temperature slowly dropped to 34°C. and a precipitate formed. The reaction mixture was flushed with nitrogen for 30 minutes and crude product recovered by filtration (101 mg., m.p. 119-124°C.). Two recrystallizations from 2:1 ethanol:water gave purified title product [24 mg.; m.p. 145-147°C.; Rf 0.56 (1:1 ethyl acetate:chloroform); m/e 256].

By the same procedure, substituting 10% fluorine in nitrogen, 5-(2-ethoxy-3-pyridyl)oxazolidine-2,4-dione is converted to 5-(5-fluoro-2-ethoxy-3-pyridyl)-oxazolidine-2,4-dione.

EXAMPLE 552-(3-Furyl)-2-Trimethylsiloxyethanenitrile

To a mixture of 3-furaldehyde (1.92 g., 20 mmoles) and about 100 mg. of zinc iodide in 25 ml. of ether, 5 trimethylsilylcarbonitrile (4.74 g., 48 mmoles) was added dropwise. The mixture was stirred about 16 hours at room temperature. The reaction mixture was washed sequentially with saturated sodium bicarbonate, water and brine, dried over anhydrous sodium sulfate, 10 filtered and evaporated in vacuo to yield 2-(3-furyl)-2-trimethylsiloxyethanenitrile [2.2 g.; pnmr/ CDCl_3 / δ : 0.2 (s, 9H); 5.4 (s, 1H); 6.4 (m, 1H); 7.3 (m, 1H); 7.5 (m, 1H)].

EXAMPLE 56

15 Ethyl 1-Hydroxy-1-(3-furyl)-
methanecarboximate Hydrochloride

2-(3-Furyl)-2-trimethylsiloxyethanenitrile (1.0 g.) was dissolved in 10 ml. of saturated ethanolic hydrogen chloride at 0-5°C. The resulting solution 20 was held at about 5°C. for 16 hours. The reaction mixture was concentrated to about half volume and diluted with ether. Filtration, with ether wash, gave ethyl 1-hydroxy-1-(3-furyl)methanecarboximate hydrochloride (746 mg.; m.p. 113-115°C.; m/e 169).

EXAMPLE 575-(3-Furyl)oxazolidine-2,4-dione

Ethyl 1-hydroxy-1-(3-furyl)methanecarboximidate hydrochloride (1.5 g., 7.5 mmoles) was combined with 50 ml. of tetrahydrofuran and triethylamine (2.21 g., 21.9 mmoles) and cooled to 10°C. Phosgene was bubbled through the cooled reaction mixture for 20 minutes. After stirring the mixture for an additional 30 minutes, nitrogen was flushed through the mixture for 10 minutes. The reaction mixture was poured slowly into 100 g. of crushed ice. The product was extracted into two portions of ether and crude product isolated as an oil by evaporation. The oil was taken up in 5 ml. of 1N sodium hydroxide and extracted with ether. The basic aqueous phase was acidified and extracted with fresh ether. Product was isolated as a gummy solid (600 mg.) by evaporation of the latter ether extract. Trituration with chloroform afforded purified 5-(3-furyl)oxazolidine-2,4-dione (109 mg.; m.p. 86-88°C.; m/e 167). Addition of hexane to the chloroform triturate gave a second crop of product (66 mg.; m.p. 86-88°C., m/e 167).

Analysis: Calcd. for $C_7H_5O_4N$:

C, 50.31; H, 3.01; N, 8.38.

Found: C, 49.97; H, 3.13; N, 8.37.

EXAMPLE 582-(5-Chloro-2-furyl)-2-trimethylsiloxyethanenitrile

5-Chloro-2-furaldehyde (2.7 g., 21 mmoles) was dissolved in 30 ml. of ether. Trimethylsilylcarbonyl nitrile (6.3 ml., 50 mmoles) and zinc iodide (about 50 mg.) were added and the mixture stirred for 1.5 hours at room temperature, at which time tlc (hexane:ethyl acetate 8:1) indicated complete reaction. Concentration to dryness afforded 2-(5-chloro-2-furyl)-2-trimethylsiloxyethanenitrile as an oil (5.5 g.; ^{1}H nmr/ $CDCl_3/\delta$: 0.3 (s, 9H); 5.4 (s, 1H); 6.1 (d, 1H); 6.5 (d, 1H)].

EXAMPLE 59

Ethyl 1-(5-chloro-2-furyl)-1-
hydroxymethanecarboximate Hydrochloride

2-(5-Chloro-2-furyl)-2-trimethylsiloxyethanenitrile
5 (2.3 g.) was dissolved in saturated ethanolic hydrogen
chloride (25 ml.) at 0°C. The solution was held for
2.5 hours at about 5°C. and then concentrated to oil.
Trituration with 20 ml. of ether afforded crystalline
ethyl 1-(5-chloro-2-furyl)-1-hydroxymethanecarboximate
10 hydrochloride (1.2 g.; m.p. 112-114°C.; m/e 203).

EXAMPLE 60

5-(5-Chloro-2-furyl)oxazolidine-2,4-dione

Ethyl 1-(5-chloro-2-furyl)-1-hydroxymethanecarbox-
imate hydrochloride (1.2 g., 5 mmoles) was suspended
15 in 50 ml. of tetrahydrofuran and cooled in an ice
bath. Following the addition of triethylamine (2.1 ml.,
15 mmoles), phosgene was bubbled into the reaction
mixture for 20 minutes, maintaining the temperature at
10 to 20°C. The mixture was flushed with nitrogen and
20 poured slowly into 100 ml. of crushed ice. The
quenched reaction mixture was extracted with 100 ml.
of ether, and the ether back-extracted with brine and
concentrated to an oil. The oil was taken up in
15 ml. of fresh ether, the solution clarified and
25 extracted with 10 ml. of 1N sodium hydroxide. The
basic extract was acidified with concentrated hydro-
chloric acid and product extracted into ethyl acetate.
After back extracting with water, the ethyl acetate
layer was concentrated to an oil (550 mg.). A portion
30 of this oil (500 mg.) was chromatographed on about
50 ml. of silica gel, with 5:1 hexane:ethyl acetate
containing 5% acetic acid as eluant. The column was

monitored by tlc (same eluant). Late eluted, product containing fractions were combined, evaporated to dryness and triturated with hexane, affording 5-(5-chloro-2-furyl)oxazolidine-2,4-dione [177 mg.; m.p. 112-114°C.; m/e 201; R_f 0.25 (5:1 hexane:ethyl acetate with 5% acetic acid)].

Analysis: Calcd. for $C_7H_4O_4NCl$:

C, 41.71; H, 2.00; N, 6.95.

Found: C, 41.80; H, 2.21; N, 6.77.

EXAMPLE 61

2-(5-Bromo-2-furyl)-2-trimethylsiloxyethanenitrile

5-Bromo-2-furaldehyde (1.1 g., 6 mmoles) was dissolved in 50 ml. of ether. A catalytic quantity (about 50 mg.) of zinc iodide was added and then trimethylsilylcarbonitrile (746 mg., 1.2 equiv.) was added dropwise. The reaction was monitored by ir (disappearance of typical carbonyl absorption) and pnmr (disappearance of typical aldehyde proton peak). After 60 minutes at room temperature, the reaction mixture was washed with saturated sodium bicarbonate, twice with water, and finally with brine, dried over anhydrous sodium sulfate and evaporated to yield 2-(5-bromo-2-furyl)-2-trimethylsiloxyethanenitrile as an oil [1.2 g.; pnmr/ $CDCl_3/\delta$: 0.3 (s, 9H); 5.6 (s, 1H); 6.4 (d, 1H); 6.6 (d, 1H)].

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EXAMPLE 62

Ethyl 1-(5-Bromo-2-furyl)-1-
hydroxymethanecarboximate Hydrochloride

Following the procedure of Example 56, except that
5 the reaction mixture was not concentrated prior to
addition of ether, 2-(5-bromo-2-furyl)-2-trimethyl-
siloxymethanenitrile (1.2 g.) was converted to ethyl 1-
(5-bromo-2-furyl)-1-hydroxymethanecarboximate
hydrochloride (480 mg., m.p. 120-122°C., m/e 247,
10 249). A less pure second crop (235 mg., m.p. 104-106°C.)
was recovered by evaporation of mother liquor and
trituration of the residue with ether.

EXAMPLE 63

5-(5-Bromo-2-furyl)oxazolidine-2,4-dione

15 Ethyl 1-(5-bromo-2-furyl)-1-hydroxymethanecarbox-
imate hydrochloride (982 mg., 3.4 mmoles) was
converted to 5-(5-bromo-2-furyl)oxazolidine-2,4-dione
[126 mg., m.p. 126-129°C., m/e 245, 247, R_f 0.2 (5:1
hexane:ethyl acetate with 5% acetic acid)] by the
20 procedure of Example 57.

EXAMPLE 64

2-(3-Bromo-2-furyl)-2-trimethylsiloxymethanenitrile

By the procedure of Example 55, 3-bromo-2-furaldehyde
(1.75 g., 10 mmoles) in 50 ml. of ether was reacted
25 with trimethylsilylcarbonitrile (8.8 ml., 70 mmoles)
in the presence of about 100 mg. of zinc iodide. At
the end of the 16 hour reaction period, the ether
supernatant was decanted from solids and evaporated to
dryness to yield 2-(3-bromo-2-furyl)-2-trimethylsiloxymethanenitrile
30 [3 g., R_f 0.7 (3:1 hexane:ethyl acetate)].

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EXAMPLE 65

Ethyl 1-(3-Bromo-2-furyl)-1-
hydroxymethanecarboximate Hydrochloride

2-(3-Bromo-2-furyl)-2-trimethoxysilylethanenitrile
5 (6.8 g.) was dissolved in 70 ml. of saturated ethanolic
hydrogen chloride at 0°C. and maintained at about 5°C.
for 2 hours. Concentration to dryness and trituration
with acetone afforded ethyl 1-(3-bromo-2-furyl)-1-
hydroxymethanecarboximate hydrochloride [4.4 g.,
10 m.p. 117-119° (dec.)].

EXAMPLE 66

5-(3-Bromo-2-furyl)oxazolidine-2,4-dione

By the procedures of Example 60, except that
phosgene was bubbled into the reaction mixture at 0 to
15 10°C., ethyl 1-(3-bromo-2-furyl)-1-hydroxymethane-
carboximate hydrochloride (4.4 g.) was converted to
purified 5-(3-bromo-2-furyl)oxazolidine-2,4-dione
[847 mg.; m.p. 128-130°C.; R_f 0.20 (5:1 hexane:ethyl
acetate containing 5% acetic acid)].

20 Analysis: Calcd. for $C_7H_4O_4NBr$:

C, 34.16; H, 1.63; N, 5.69.

Found: C, 34.30; H, 1.88; N, 5.67.

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EXAMPLE 67

2-(2-Furyl)-2-trimethylsiloxyethanenitrile

2-Furaldehyde (24 g., 0.25 mole) was cooled to 0-5°C., zinc iodide (500 mg.) was added and the mixture stirred. Trimethylsilylcarbonitrile (30 ml.) was added dropwise. The mixture was allowed to warm to room temperature and stirred for approximately 64 hours at room temperature. The reaction mixture was diluted with methylene chloride, extracted twice with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, treated with activated carbon, filtered and evaporated to yield 2-(2-furyl)-2-trimethylsiloxyethanenitrile as an oil [36 g., 74%; pnmr/ CDCl_3 /delta: 0.2 (s, 9H); 5.6 (s, 1H); 6.4 (m, 1H); 6.6 (m, 1H); 7.4 (d, 1H)].

EXAMPLE 68

Ethyl 1-(2-Furyl)-1-hydroxymethanecarboximidate

Following the procedure of Example 56, 2-(2-furyl)-2-trimethylsiloxyethanenitrile (15 g.) was reacted with saturated ethanolic hydrogen chloride, except that a reaction time of about two hours was employed. Crude product was isolated by evaporating the reaction mixture to an oil. The oil was partitioned in 400 ml. of chloroform and saturated sodium bicarbonate. The chloroform was washed twice with fresh saturated sodium bicarbonate, washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to yield ethyl 1-(2-furyl)-1-hydroxymethanecarboximidate as an oil [10.6 g., 81%; pnmr/ CDCl_3 /delta: 1.3 (t, 3H); 4.1 (q, 2H); 5.1 (s, 1H); 4.8-5.2 (m, 1H); 6.3 (m, 2H); 7.3 (d, 1H)].

EXAMPLE 695-(2-Furyl)oxazolidine-2,4-dione

Ethyl 1-(2-furyl)-1-hydroxymethanecarboximidate (10.5 g., 6.2 mmoles) was dissolved in 125 ml. of stirring tetrahydrofuran and cooled to 0-5°C. Triethylamine (12.5 g., 0.124 mole) was added and the cold solution then perfused with phosgene for 35 minutes, warmed to room temperature and stirred for an additional 16 hours. The reaction mixture was slowly poured into 1 liter of ice and water. The product was extracted into 3 portions of ethyl acetate. The extracts were combined and product extracted into 4 portions of 1N sodium hydroxide. The combined aqueous extracts were acidified with 6N hydrochloric acid, and product extracted into 4 portions of chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate, treated with activated carbon, filtered and evaporated to yield crude product as an oil (2.1 g.). Column chromatography on 100 g. of silica gel with 2:1 chloroform:ethyl acetate as eluant in 10 ml. fractions, monitored by tlc, gave, by evaporation of fractions 36-48, purified 5-(2-furyl)oxazolidine-2,4-dione (281 mg.; m.p. 99-102°C.; m/e 167). Recrystallization from toluene gave more highly purified product (235 mg., m.p. 101-103°C.).

Analysis: Calcd. for $C_7H_5O_4N$:

C, 50.31; H, 3.02; N, 8.38.

Found: C, 50.41; H, 3.25; N, 8.28.

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EXAMPLE 70

5-Hydroxy-5-(3-methoxy-2-furyl)-
2,4,6(1H,3H,5H)-pyrimidinetrione

3-Methoxyfuran (3.5 g., approximately 50% pure
5 from Preparation 10), alloxan hydrate [5,5-dihydroxy-
2,4,6(1H,3H,5H)-pyrimidinetrione, 4.8 g.] and 75 ml.
of ethanol were combined and refluxed for 1 hour. The
reaction mixture was cooled to room temperature and
concentrated to dryness. Trituration of the residue
10 with 25 ml. of water afforded 5-hydroxy-5-(3-methoxy-
2-furyl)-2,4,6(1H,3H,5H)-pyrimidinetrione [1.9 g.,
m.p. 120-130 (dec.), m/e 240].

EXAMPLE 71

5-(3-Methoxy-2-furyl)oxazolidine-2,4-dione

15 5-Hydroxy-5-(3-methoxy-2-furyl)-2,4,6(1H,3H,5H)-
pyrimidinetrione (1.7 g.) was stirred with 1N sodium
hydroxide (14 ml., 14 mmoles) for 20 minutes. The
reaction mixture was acidified with acetic acid and
product extracted into ethyl acetate and isolated in
20 crude form by evaporation to an oil. Chromatography
on ca. 100 ml. of silica gel, monitored by tlc,
afforded 5-(3-methoxy-2-furyl)oxazolidine-2,4-dione
[470 mg., m.p. 102-104°C., R_f 0.6 (1:1 hexane:ethyl
acetate with 5% acetic acid)].

25 EXAMPLE 72

2-(5-Phenyl-2-thienyl)-2-
trimethylsiloxyethanenitrile

5-Phenyl-2-thenaldehyde (0.9 g.) in 35 ml. of
ether was reacted with 1 ml. of trimethylsilylcarbo-
30 nitrile in the presence of about 50 mg. of zinc iodide.
After 1 hour of stirring at room temperature, tlc
indicated reaction was complete. Evaporation to
dryness gave 2-(5-phenyl-2-thienyl)-2-trimethylsiloxy-
ethanenitrile [1.65 g., R_f 0.5 (5:1 hexane:ethyl
35 acetate with 5% acetic acid)].

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EXAMPLE 73

Ethyl 1-Hydroxy-1-(5-phenyl-2-thienyl)-
methanecarboximidate Hydrochloride

2-(5-Phenyl-2-thienyl)-2-trimethylsiloxyethane-
nitrile (1.6 g.) was dissolved in 30 ml. of cold,
saturated ethanolic hydrogen chloride and maintained
at 0 to 5°C. for about 17 hours. The reaction mixture
was evaporated to dryness and triturated with ethyl
acetate to yield ethyl 1-hydroxy-1-(5-phenyl-2-thienyl)-
methanecarboximidate hydrochloride [0.9 g.; pnmr/DMSO/
delta: includes 1.1 (3H); 4.0 (2H); 5.2 (1H); 6.5
(1H)].

EXAMPLE 74

5-(5-Phenyl-2-thienyl)oxazolidine-2,4-dione

Ethyl 1-hydroxy-1-(5-phenyl-2-thienyl)methane-
carboximidate hydrochloride (790 mg., 2.6 mmoles) and
triethylamine (1.4 ml., 10 mmoles) were reacted with
phosgene and product isolated according to the pro-
cedures of Example 12, except that the eluant in the
chromatography was 2:1 ethyl acetate:hexane, affording
5-(5-phenyl-2-thienyl)oxazolidine-2,4-dione (172 mg.,
m.p. 233-235°C.).

Analysis: Calcd. for $C_{13}H_9O_3NS$:

C, 60.23; H, 3.50; N, 5.40.

Found: C, 59.94; H, 3.65; N, 5.38.

EXAMPLE 75

2-(2-Thienyl)-2-trimethylsiloxyethanenitrile

By the procedure of Example 67, 2-thenaldehyde
(56.1 g., 46.8 ml., 0.5 mole) was reacted for 16 hours
with trimethylsilylcarbonitrile (60 ml.) in the
presence of zinc iodide (approximately 0.5 g.),
yielding 2-(2-thienyl)-2-trimethylsiloxyethanenitrile
as an oil [92 g.; m/e 211; pnmr/ $CDCl_3$ /delta: 0.2 (s,
9H); 5.8 (s, 1H); 6.9-7.5 (m, 3H)].

EXAMPLE 76Ethyl 1-Hydroxy-1-(2-thienyl)methanecarboximidate2-(2-Thienyl)-2-trimethylsiloxyethanenitrile

(45 g.) was dissolved in 450 ml. of absolute ethanol.

- 5 The solution was cooled to 0-5°C. and perfused with hydrogen chloride for 40 minutes. The mixture was kept at about 5°C. for 16 hours and evaporated to dryness. The residue was triturated with four 200 ml. portions of ether, and then partitioned between 400 ml. 10 of methylene chloride and saturated sodium bicarbonate. The organic phase was washed twice with saturated sodium bicarbonate, treated with activated carbon, filtered and concentrated to yield ethyl 1-hydroxy-1-(2-thienyl)methanecarboximidate as an oil which 15 solidified on standing [10 g.; pnmr/ CDCl_3/δ : 1.2 (t, 3H); 4.1 (q, 2H); 5.2 (s, 1H), 5.9 (s, 1H); 6.8-7.3 (m, 3H); 7.3-8.1 (s, 1H)].

EXAMPLE 775-(2-Thienyl)oxazolidine-2,4-dioneEthyl 1-hydroxy-1-(2-thienyl)methanecarboximidate

- 10 (10 g., 5.4 mmoles) and triethylamine (15.1 ml., 10.8 mmoles) were dissolved in 100 ml. of tetrahydrofuran. The solution was cooled to 0-5°C. and perfused with phosgene for 45 minutes. Stirring was continued for an additional 5 hours at 0-5°C. The reaction mixture was poured slowly over 1500 ml. of crushed 25 ice. The product was extracted into 1.1 liter of ethyl acetate in three portions. The combined ethyl acetate extracts were then extracted twice with saturated sodium bicarbonate and once with 1:1 saturated sodium carbonate:water. The combined bicarbonate and 30 carbonate washes were acidified to pH 1-2 with 6N hydrochloric acid and product extracted into several portions of ether. The combined ether extracts were washed with brine, dried over anhydrous magnesium sulfate, treated with activated charcoal, filtered and 35 evaporated to yield product (3.0 g.). Recrystallization from toluene afforded 5-(2-thienyl)oxazolidine-2,4-dione (1.8 g.; m.p. 138-140°C., m/e 183).

Analysis: Calcd. for $\text{C}_7\text{H}_5\text{NO}_3\text{S}$:

C, 45.89; H, 2.75; N, 7.65.

40 Found: C, 45.99; H, 2.87; N, 7.62.

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EXAMPLE 78

2-(3-Methyl-2-thienyl)-2-trimethylsiloxyethanenitrile

Following the procedure of Example 67, 3-methyl-2-thenaldehyde (31.6 g., 0.25 mole) was reacted with trimethylsilylcarbonitrile (30 ml.) for 16 hours in the presence of 500 mg. of zinc iodide. The reaction mixture was diluted with 200 ml. of methylene chloride and further isolated also according to Example 13, affording 2-(3-methyl-2-thienyl)-2-trimethylsiloxyethanenitrile [52 g., 93%; $\text{pnmr}/\text{CDCl}_3/\delta$: 0.2 (s, 9H); 2.3 (s, 3H); 5.7 (s, 1H); 6.8 (d, 1H); 7.25 (d, 1H)].

EXAMPLE 79

Ethyl 1-Hydroxy-1-(3-methyl-2-thienyl)methanecarboximate

2-(3-Methyl-2-thienyl)-2-trimethylsiloxyethanenitrile (13 g.) was added dropwise to 100 ml. of cold ethanol, saturated with hydrogen chloride, keeping the temperature at 0-4°C. After 1 hour at 0-4°C., the reaction mixture was evaporated to dryness. The residue was triturated three times with 100 ml. portions of ether, and then partitioned between 300 ml. of methylene chloride and saturated sodium bicarbonate. The separated methylene chloride layer was washed with two additional portions of saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and evaporated to yield ethyl 1-hydroxy-1-(3-methyl-2-thienyl)methanecarboximate (8.0 g., 69%; m.p. 73-76°C.; m/e 199).

EXAMPLE 805-(3-Methyl-2-thienyl)oxazolidine-2,4-dione

Ethyl 1-hydroxy-1-(3-methyl-2-thienyl)methane-carboximate (6.0 g., 0.03 mole) was dissolved in 75 ml. of tetrahydrofuran and cooled to 0-5°C. Triethylamine (6.07 g., 8.37 ml., 0.06 mole) was added, the solution was perfused with phosgene for 35 minutes, and poured slowly into 1 liter of ice and water. The product was extracted into three portions of ethyl acetate. The ethyl acetate extracts were combined and product extracted into four portions of saturated sodium bicarbonate. The combined aqueous extracts were acidified with 6N hydrochloric acid and product reextracted into 3 portions of fresh ethyl acetate. The combined fresh organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to yield product as an oil (2.4 g., 41%), which crystallized on scratching. Recrystallization from toluene gave purified 5-(3-methyl-2-thienyl)oxazolidine-2,4-dione (1.84 g., 31% overall; m.p. 119-121°C., m/e 197).

Analysis: Calcd. for $C_8H_7O_3NS$:

C, 48.72; H, 3.58; N, 7.10.

Found: C, 48.65; H, 3.58; N, 7.01.

A second crop of product (0.63 g.) was obtained by extraction of the initial ethyl acetate extracts with 3 portions of 1N sodium hydroxide, followed by further isolation as above.

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EXAMPLE 81

2-(5-Methyl-2-thienyl)-

2-trimethylsiloxyethanenitrile

5-Methyl-2-thienaldehyde (25 g., 0.2 mole), zinc
5 iodide (266 mg.) and 100 ml. of ether were combined
and stirred at room temperature. Trimethylsilylcarbo-
nitrile (23.5 g., 0.24 mole) was added dropwise and
the reaction mixture stirred for an additional 2 hours.
The reaction mixture was diluted with 100 ml. of
10 ether, washed with two 50 ml. portions of 5% sodium
bicarbonate, washed with two 25 ml. portions of brine,
dried over anhydrous magnesium sulfate, filtered and
evaporated to dryness to produce 2-(5-methyl-2-thienyl)-
2-trimethylsiloxyethanenitrile [42 g.; $\text{pnmr}/\text{CDCl}_3/\delta$:
15 0.2 (s, 9H); 2.2 (s, 3H); 5.6 (s, 1H); 6.6-7.4 (m,
2H)].

EXAMPLE 82

Ethyl 1-Hydroxy-1-(5-methyl-2-thienyl)-
methanecarboximidate Hydrochloride

20 With cooling to 0-5°C., ethanol (550 ml.) was
saturated with hydrogen chloride. 2-(5-Methyl-2-
thienyl)-2-trimethylsiloxyethanenitrile (42 g.) was
dissolved in portions and the solution maintained at
0°C. for 2.5 hours. The reaction mixture was evaporated
25 to dryness and the residue triturated with diethyl
ether to provide ethyl 1-hydroxy-1-(5-methyl-2-thienyl)-
methanecarboximidate hydrochloride [33 g.; m.p.
122-123°C., $\text{pnmr}/\text{DMSO}/\delta$: 1.1-1.6 (3H); 2.5 (3H);
4.6 (2H); 5.9 (1H); 6.6-7.2 (2H)].

EXAMPLE 835-(5-Methyl-2-thienyl)oxazolidine-2,4-dione

Ethyl 1-hydroxy-1-(5-methyl-2-furyl)methane-carboximidate hydrochloride (10 g., 0.042 mole) was
5 combined with triethylamine (14.1 g., 0.14 mole) in
250 ml. of tetrahydrofuran and cooled to 0-5°C. The
cold reaction mixture was perfused with phosgene for
30 minutes, warmed to room temperature and poured
portionwise onto about 275 ml. of crushed ice. The
10 product was extracted into two 200 ml. portions of
ethyl acetate. The ethyl acetate extracts were
combined and extracted with two 150 ml. portions of 1N
sodium hydroxide. The combined aqueous extracts were
acidified with hydrochloric acid and then extracted
15 with two 250 ml. portions of fresh ethyl acetate. The
last, combined organic extracts were dried over
anhydrous magnesium sulfate, filtered and evaporated
to yield 5-(5-methyl-2-thienyl)oxazolidine-2,4-dione
(7.2 g.). Recrystallization from chloroform/hexane
20 gave purified product (910 mg.; m.p. 108-109°C.; m/e
197).

EXAMPLE 842-(5-Chloro-2-thienyl)-2-trimethylsiloxyethanenitrile

5-Chlorothenaldehyde (5 g., 34 mmoles) was combined with zinc iodide (50 mg.) and 30 ml. of diethyl ether and cooled to 0°C. Trimethylsilylcarbonitrile (4.04 g., 40 mmoles) was added dropwise and the reaction mixture warmed to room temperature and stirred for 4 hours. Additional equal portions of trimethylsilylcarbonitrile and zinc iodide were added and the reaction stirred an additional 16 hours. The reaction mixture was diluted with ether, washed with two 30 ml. portions of 5% sodium bicarbonate, washed once with 30 ml. of brine, dried over anhydrous magnesium sulfate and evaporated to yield 2-(5-chloro-2-thienyl)-2-trimethylsiloxyethanenitrile as an oil [4.0 g., $\text{pnmr}/\text{CDCl}_3/\delta$: 0.3 (s, 9H); 5.7 (s, 1H); 7.0 (q, 2H)].

By the same method, 3-fluoro-2-thenaldehyde, 4-fluoro-2-thenaldehyde, 5-fluoro-2-thenaldehyde, 5-fluoro-3-thenaldehyde [Gronowitz and Rosen, Chem. Ser. 1, pp. 33-43 (1971); Chem. Abstracts 75, 20080c], 4-fluoro-3-thenaldehyde, 4-methoxy-3-thenaldehyde, and 4-methylthio-3-thenaldehyde are converted, respectively, to 2-(3-fluoro-2-thienyl)-2-trimethylsiloxyethanenitrile, 2-(4-fluoro-2-thienyl)-2-trimethylsiloxyethanenitrile, 2-(5-fluoro-2-thienyl)-2-trimethylsiloxyethanenitrile, 2-(5-fluoro-3-thienyl)-2-trimethylsiloxyethanenitrile, 2-(4-fluoro-3-thienyl)-2-trimethylsiloxyethanenitrile, 2-(4-methoxy-3-thienyl)-2-trimethylsiloxyethanenitrile, 2-(4-methylthio-3-thienyl)-2-trimethylsiloxyethanenitrile.

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EXAMPLE 85

Ethyl 1-(5-Chloro-2-thienyl)-1-hydroxymethanecarboximidate Hydrochloride

2-(5-Chloro-2-thienyl)-2-trimethylsiloxyethane-
 5 nitrile (4 g.) was dissolved in absolute ethanol
 (100 ml.). The solution was cooled to 0-5°C. and
 saturated with hydrogen chloride. The reaction mixture
 was held for 16 hours at 0°C., evaporated to dryness
 and triturated with ether to yield solid ethyl 1-(5-
 10 chloro-2-thienyl)-1-hydroxymethanecarboximidate hydro-
 chloride [3 g., pnmr/DMSO/delta: 1.2 (3H); 4.2 (2H);
 5.3 (1H); 6.6 (1H); 6.9 (1H); 7.4 (1H); 8.4 (1H)].

By the same method, the other nitriles of the
 preceding Example are converted to ethyl 1-(3-fluoro-
 15 2-thienyl)-1-hydroxymethanecarboximidate hydrochloride,
 ethyl 1-(4-fluoro-2-thienyl)-1-hydroxymethanecarbox-
 imidate hydrochloride, ethyl 1-(5-fluoro-2-thienyl)-1-
 hydroxymethanecarboximidate hydrochloride, ethyl 1-(5-
 fluoro-3-thienyl)-1-hydroxymethanecarboximidate
 20 hydrochloride, ethyl 1-(4-fluoro-3-thienyl)-1-hydroxy-
 methanecarboximidate hydrochloride, ethyl 1-hydroxy-1-
 (4-methoxy-3-thienyl)methanecarboximidate hydrochloride
 and 1-hydroxy-1-(4-methylthio-3-thienyl)methanecarbox-
 imidate hydrochloride.

EXAMPLE 865-(5-Chloro-2-thienyl)oxazolidine-2,4-dione

5 Ethyl 1-(5-chloro-2-thienyl)-1-hydroxymethane-
carboximate hydrochloride (3.0 g., 12 mmoles) and
triethylamine (4.0 g., 39 mmoles) were combined in
90 ml. of tetrahydrofuran and cooled to 0°C. The
slurry was perfused with phosgene for 30 minutes,
warmed to room temperature and stirred for 16 hours.
The reaction mixture was poured slowly into 100 ml.
10 of crushed ice and product extracted into two 100 ml.
portions of ethyl acetate. The combined ethyl acetate
extracts were back-washed with two 50 ml. portions of
water and one 50 ml. portion of saturated sodium
chloride, dried over anhydrous magnesium sulfate,
15 filtered and evaporated to a semi-solid (2.5 g.).
Recrystallization from toluene provided purified 5-(5-
chloro-2-thienyl)oxazolidine-2,4-dione (0.6 g., m.p.
126-130°C.).

Analysis: Calcd. for $C_7H_4O_3NClS$:

20 C, 38.64; H, 1.84; N, 6.44.

Found: C, 38.17; H, 2.07; N, 6.91.

By the same method the other imino ethers of the
preceding Example are converted to 5-(3-fluoro-2-
thienyl)oxazolidine-2,4-dione, 5-(4-fluoro-2-thienyl)-
25 oxazolidine-2,4-dione, 5-(5-fluoro-2-thienyl)oxazolidine-
2,4-dione, 5-(5-fluoro-3-thienyl)oxazolidine-2,4-
dione, 5-(4-fluoro-3-thienyl)oxazolidine-2,4-dione, 5-
(4-methoxy-3-thienyl)oxazolidine-2,4-dione and 5-(4-
methylthio-3-thienyl)oxazolidine-2,4-dione.

EXAMPLE 872-(4-Bromo-3-thienyl)-2-trimethylsiloxyethanenitrile

4-Bromo-3-thenaldehyde (5.5 g., 29 mmoles) in 75 ml. of methylene chloride was cooled to 0-5°C. Zinc iodide (50 mg.) was added, followed by the dropwise addition of trimethylsilylcarbonitrile (3.47 g., 35 mmoles) over a 3 minute period. The mixture was warmed to room temperature, stirred for 16 hours, washed twice with saturated sodium bicarbonate, washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated to yield 2-(4-bromo-3-thienyl)-2-trimethylsiloxyethanenitrile as an oil (7.6 g., 90%, m/e 291/289).

EXAMPLE 88

15 Ethyl 1-(4-Bromo-3-thienyl)-
 1-hydroxymethanecarboximidate

2-(4-Bromo-3-thienyl)-2-trimethylsiloxyethanenitrile (7.5 g.) in 200 ml. of ethanol, cooled in an ice bath, was perfused with hydrogen chloride for 45 minutes. After an additional 20 minutes at 0-5°C. the reaction mixture was evaporated to dryness and triturated with ether to yield the hydrochloride salt of the product as a hygroscopic solid. The salt was taken up in a mixture of methylene chloride and saturated sodium bicarbonate. The separated methylene chloride layer was washed twice with saturated sodium bicarbonate, washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated to yield ethyl 1-(4-bromo-3-thienyl)-1-hydroxymethanecarboximidate as an oil (6.1 g., 89%, m/e 265/263).

EXAMPLE 895-(4-Bromo-3-thienyl)oxazolidine-2,4-dione

5 Ethyl 1-(4-bromo-3-thienyl)-1-hydroxymethane-
carboximate (6.0 g., 23 mmoles) and triethylamine
(5.15 g., 51 mmoles) were combined in 250 ml. of
tetrahydrofuran, cooled in an ice-water bath and
perfused with phosgene for 35 minutes. The reaction
mixture was warmed to room temperature, stirred for
1.5 hours, poured slowly over 1 liter of crushed ice,
10 and product extracted into 3 portions of methylene
chloride. The combined methylene chloride extracts
were evaporated to an oil, crystallized by the addition
of a small amount of ether and hexane, and triturated
in about 40 ml. of ether to yield 5-(4-bromo-3-thienyl)-
15 oxazolidine-3,4-dione (3.4 g., 56%; m.p. 158-161°C.).
Recrystallization from 40 ml. of toluene afforded
purified product (2.51 g.; m.p. 164-166°C.; m/e 263/261).

Alternatively, the ether solution of the lithium
derivative of 3,4-dibromothiophene is reacted with a
20 1.05 equivalent of alloxan according to the procedure
of Example 54, yielding 5-(4-bromo-3-thienyl)-5-
hydroxy-2,4,6(1H,3H,5H)-pyrimidinetrione. Following
the procedure of Example 55, the latter is converted
to the desired 5-(4-bromo-3-thienyl)oxazolidine-2,4-
25 dione.

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EXAMPLE 902-(3-Thienyl)-2-trimethylsiloxyethanenitrile

3-Thenaldehyde (10 g., 0.089 moles), zinc iodide (120 mg.) and ether (60 ml.) were combined and stirred. 5 Trimethylsilylcarbonitrile (10.6 g., 0.107 mole) was added dropwise over 10 minutes and the reaction mixture stirred for 16 hours, diluted with 60 ml. of ether, washed with two 30 ml. portions of 5% sodium bicarbonate, washed with 30 ml. of brine, dried over anhydrous 10 magnesium sulfate, filtered and evaporated to yield 2-(3-thienyl)-2-trimethylsiloxyethanenitrile as an oil [14.3 g., pnmr/ CDCl_3/δ : 0.2 (9H); 5.6 (1H); 7.0-7.5 (3H)].

EXAMPLE 91Ethyl 1-Hydroxy-1-(3-thienyl)methanecarboximidate

At 0-5°C., 2-(3-thienyl)-2-trimethylsiloxyethanenitrile (14.3 g.) was dissolved portionwise in 500 ml. of ethanol, previously saturated with hydrogen chloride at 0-5°C. The solution was held at 0°C. for 16 hours, 20 and the product isolated as the hydrochloride salt by evaporation of the reaction mixture to dryness and trituration of the residue with ether. The salt was taken up in 400 ml. of chloroform and 100 ml. of saturated sodium bicarbonate. The separated chloroform 25 layer was washed with an additional 100 ml. of saturated sodium bicarbonate, washed with brine, dried over magnesium sulfate, filtered and evaporated to yield ethyl 1-hydroxy-1-(3-thienyl)methanecarboximidate [12.5 g., pnmr/ CDCl_3/δ : 1.0-1.3 (3H); 4.8-5.3 30 (2H); 5.0 (1H); 6.9-7.2 (3H), 7.3-8.0 (1H)].

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EXAMPLE 92

5-(3-Thienyl)oxazolidine-2,4-dione

Ethyl 1-hydroxy-1-(3-thienyl)methanecarboximate
(12.5 g., 0.067 mole) and triethylamine (16.1 g.,
5 0.159 mole) were combined in 600 ml. of tetrahydrofuran
and cooled to 0°C. The mixture was perfused with
phosgene for 30 minutes, warmed to room temperature
and allowed to stand for 16 hours. The mixture was
poured slowly into 600 ml. of ice and water (foaming
10 of excess phosgene), and extracted twice with 600 ml.
portions of ethyl acetate. The combined extracts were
washed with two 300 ml. portions of 1N sodium hydroxide.
The combined basic extracts were acidified with hydro-
chloric acid and product re-extracted into two fresh
15 300 ml. portions of ethyl acetate. The combined fresh
extracts were dried over anhydrous magnesium sulfate,
filtered and evaporated to solids (8.0 g.). Recrystal-
lization from hot toluene gave purified 5-(3-thienyl)-
oxazolidine-2,4-dione (5.5 g., m.p. 133-136°C.). A
20 second recrystallization, from ethyl acetate/hexane,
provided additional purification (first crop: 2.352 g.;
m.p. 136-138°C., m/e 183; ir (KBr): 5.5, 5.8 microns).

EXAMPLE 93Ethyl 2-Hydroxy-2-(3-thienyl)acetate

3-Thenaldehyde (10 g., 0.089 mole) and sodium bisulfite (13.8 g., 0.133 mole) were heated at 50-60°C., in 152 ml. of water for 2 hours, forming the bisulfite adduct in situ. The reaction mixture was cooled to 5°C., and 200 ml. of ethyl acetate was added. To the stirred, two phase system, potassium cyanide (17.4 g., 0.267 mole) in 75 ml. of water was added dropwise over 30 minutes. The reaction mixture was warmed to 20°C. and held for 1 hour. Additional potassium cyanide (5.7 g., 0.088 mole) was added and the mixture stirred an additional 10 minutes at 20°C. The layers were separated and the aqueous layer-washed with 50 ml. of ethyl acetate. The combined ethyl acetate layers were washed with saturated sodium chloride, providing a clean solution of the cyanohydrin of 3-thenaldehyde in ethyl acetate.

The solution of the cyanohydrin of 3-thenaldehyde in ethyl acetate was stirred at room temperature and charged with 41.6 g. (52.7 ml., 10 equiv.) of ethanol and concentrated hydrochloric acid (15.2 ml., 0.182 mole) and the mixture refluxed for 17 hours. The reaction mixture was cooled to 25°C., washed with 100 ml. of water and then with saturated sodium bicarbonate to a pH >7.0, dried over anhydrous magnesium sulfate, treated with activated carbon, filtered and evaporated to an oil (approximately 11.5 g.) which upon addition of 46 ml. of 1:1 toluene/isooctane afforded crystalline ethyl 2-hydroxy-2-(3-thienyl)acetate (7.4 g., 45%, m.p. 55-57°C.).

EXAMPLE 942-Hydroxy-2-(3-thienyl)acetamide

Ethyl 2-hydroxy-2-(3-thienyl)acetate (168 g., 0.903 mole) was slurried in 15N ammonium hydroxide (420 ml., 6.3 moles) and heated to reflux for 2.5 hours. The resulting solution was cooled to 70°C. and toluene (840 ml.) was added. The stirred mixture was allowed to cool to 20°C. and granulated for 1 hour. Filtration, with toluene wash, gave 2-hydroxy-2-(3-thienyl)acetamide (105.9 g., 75%, m.p. 120-126°C.). A second crop (10.3 g., m.p. 114-120°C.) was obtained by evaporating the aqueous layer of the filtrate to 50 ml. and granulating with 100 ml. of toluene. Recrystallization of the first and second crops from ethyl-acetate afforded a 77-79% recovery of purified product (m.p. 127-130°C.).

EXAMPLE 955-(3-Thienyl)oxazolidine-2,4-dione

At 25°C., 2-hydroxy-2-(3-thienyl)acetamide (10.0 g., 0.064 mole) was added to a solution of sodium methoxide (10 g., 0.185 mole) and diethyl carbonate (22.0 ml., 0.182 mole) in 200 ml. of ethanol. The reaction mixture was heated to reflux for 3 hours, cooled to 20°C., and slowly diluted with 100 ml. of water. Ethanol was removed by evaporation and the aqueous residue treated with activated carbon and filtered. The filtrate was layered with ethyl acetate and the pH adjusted to 1.0 with concentrated hydrochloric acid. The aqueous layer was separated and washed with 100 ml. of ethyl acetate. The combined ethyl acetate layers were dried over anhydrous magnesium sulfate. The ethyl acetate was removed by distillation in vacuo with displacement by toluene to a final volume of 150 ml. The resulting slurry was heated to reflux (solution), cooled to 0°C., and filtered to yield 5-(3-thienyl)oxazolidine-2,4-dione (8.92 g., 76.5%, m.p. 135-138°C.).

EXAMPLE 96

Sodium 5-(3-Thienyl)oxazolidine-2,4-dione

5-(3-Thienyl)oxazolidine-2,4-dione (3.0 g., 16.4 mmole) was dissolved in 60 ml. of ethyl acetate and treated with 300 mg. of activated carbon. After stirring at 20°C. for 10 minutes, the mixture was filtered with ethyl acetate wash. Methanolic sodium hydroxide (3.78N, 4.2 ml.) was added and the sodium salt was allowed to crystallize. After about 30 minutes, 0.3 ml. of water was added. The slurry was granulated for 30 minutes at room temperature, then cooled to 5°C. and granulated for an additional 30 minutes. Filtration gave sodium 5-(3-thienyl)oxazolidine-2,4-dione as the monohydrate (3.37 g., 95%, m.p. 208-210°C.).

Analysis: Calcd. for $C_7H_4O_3NSNa.H_2O$:

C, 37.67; H, 2.71; N, 6.28; O, 28.67; S, 14.37;
Na, 10.30; H_2O , 8.07.

Found: C, 37.35; H, 3.03; N, 6.24; O, 27.83; S, 14.33;
Na, 10.76; H_2O , 8.30.

Sodium hydroxide is substituted with an equivalent of potassium hydroxide, diethanolamine, meglumine or piperazine to produce the corresponding salts. The solvent is removed by evaporation or a non-solvent such as ether or hexane is added as necessary to facilitate precipitation of the product.

The same methods are employed to produce the pharmaceutically acceptable salts of the other oxazolidine-2,4-diones of the present invention.

EXAMPLE 972-(3-Bromo-2-thienyl)-2-trimethylsiloxyethanenitrile

5 3-Bromo-2-thenaldehyde (6 g., 31 mmoles) and zinc
iodide (50 mg.) were combined with 180 ml. of methylene
chloride. Trimethylsilylcarbonitrile (4.0 g., 5.2 ml.,
41 mmoles) were added dropwise. The reaction mixture
was stirred for 24 hours at room temperature, diluted
with 50 ml. of methylene chloride, washed with 60 ml.
10 of 5% sodium bicarbonate and then with 50 ml. of
brine, dried over anhydrous magnesium sulfate, filtered
and evaporated to yield 2-(3-bromo-2-thienyl)-2-
trimethylsiloxyethanenitrile (7.2 g., oil, m/e 291/289).

EXAMPLE 98

Ethyl 1-(3-Bromo-2-thienyl)-1-

hydroxymethanecarboximidate Hydrochloride

15 At 0°C., 2-(3-bromo-2-thienyl)-2-trimethylsiloxy-
ethanenitrile (7.0 g., 24 moles) was dissolved in
210 ml. of ethanol saturated at 0°C. with hydrogen
20 chloride. After stirring for 30 minutes at the same
temperature, the reaction mixture was evaporated to
dryness. Trituration of the solid residue with ether
afforded ethyl 1-(3-bromo-2-thienyl)-1-hydroxymethane-
carboximidate hydrochloride (7.0 g., m.p. 120-122°C.).

EXAMPLE 995-(3-Bromo-2-thienyl)oxazolidine-2,4-dione

Ethyl 1-(2-bromo-2-thienyl)-1-hydroxymethane-carboximate hydrochloride (6.8 g., 23 mmoles) and triethylamine (7.6 g., 10.5 ml., 76 mmoles) were combined in 250 ml. of tetrahydrofuran. The mixture was cooled to 0-5°C., perfused with phosgene for 30 minutes, warmed to room temperature, stirred for 16 hours, and poured slowly into 300 ml. of crushed ice. The quenched reaction mixture was extracted twice with 200 ml. portions of chloroform. The combined chloroform extracts were washed with 60 ml. of brine, dried over anhydrous magnesium sulfate, filtered and evaporated to an oil. Addition of hexane and ether afforded crystalline product. Recrystallization from toluene gave 5-(3-bromo-2-thienyl)oxazolidine-2,4-dione (2.25 g.; m.p. 138-139°C.).

Analysis: Calcd. for $C_7H_4O_3NSBr$:

C, 32.09; H, 1.59; N, 5.34; S, 12.21.

Found: C, 32.41; H, 1.75; N, 5.49; S, 12.61.

EXAMPLE 1005-(5-Bromo-2-thienyl)-2-thioxooxazolidin-4-one

Potassium cyanide (7.9 g., 0.123 mole) and potassium thiocyanate (10 g., 0.104 mole) were combined in 8.5 ml. of water and stirred at 0°C. 5-Bromo-2-thienaldehyde (20 g., 0.104 mole) was added, yielding a slurry. Hydrochloric acid (30%, 50.7 ml.) was added, producing an oil ball. The reaction mixture was diluted with 104 ml. of water and stirred for 48 hours, by which time a granular solid had formed. Solids were recovered by filtration and distributed between chloroform and 5% sodium bicarbonate. The mixture was filtered, and the aqueous layer separated, acidified and the precipitated product recovered by filtration. Recrystallization from toluene gave purified 5-(5-bromo-2-thienyl)-2-thioxooxazolidin-4-one (2.08 g., m.p. 119-120°C., m/e 279/277).

Analysis: Calcd. for $C_7H_4BrNO_2S_2$:

C, 30.23; H, 1.95; N, 5.04.

Found: C, 30.54; H, 1.72; N, 5.26.

EXAMPLE 1015-(5-Bromo-2-thienyl)oxazolidine-2,4-dione5-(5-Bromo-2-thienyl)-2-thioxooxazolidin-4-one

(1.5 g.) was dissolved in 1:1 water:ethanol (10 ml.)
 5 at 50°C. Hydrogen peroxide (30%, 7.0 ml.) was added
 to the stirred solution, which became somewhat turbid.
 Turbidity was reduced by the addition of 1 ml. of
 ethanol. The mixture was heated at 70°C. for 30 minutes,
 cooled somewhat, diluted with 100 ml. water and extracted
 10 with chloroform. The chloroform extract was washed
 with two 50 ml. volumes of sodium bicarbonate. The
 combined aqueous extracts were clarified by filtration,
 acidified with hydrochloric acid to pH 1.0, and filtered
 to yield 5-(5-bromo-2-thienyl)oxazolidine-2,4-dione
 15 (0.51 g., 36%; m.p. 139-139.5°C.; m/e 263/261).

Analysis: Calcd. for $C_7H_4BrNO_3S$:

C, 32.08; H, 1.54; N, 5.34.

Found: C, 32.16; H, 1.69; N, 5.47.

EXAMPLE 102

5-Hydroxy-5-(3-methoxy-2-thienyl)-
2,4,6(1H,3H,5H)-pyrimidinetrione

3-Methoxythiophene [2.4 g., crude material prepared
 according to Arkiv. Kemi. 12, 239-246 (1958); Chem.
 Abstr. 52, 20115d] and alloxan hydrate (3.2 g.) were
 25 dissolved by heating in 25 ml. of ethanol. Hydrochloric
 acid (1N, 3 ml., 3 mmoles) was added and the mixture
 refluxed for 3 minutes. The mixture was cooled to
 room temperature and diluted with 15 ml. of water to
 induce further crystallization of product. Filtration
 30 with 1:1 ethanol:water and then water wash gave 5-
 hydroxy-5-(3-methoxy-2-thienyl)2,4,6(1H,3H,5H)-pyrimidine-
 trione [1.5 g., m.p. 190-210°C. (dec.); R_f 0.3 (1:1
 hexane:ethyl acetate with 5% acetic acid); m/e 256].

EXAMPLE 1035-(3-Methoxy-2-thienyl)oxazolidine-2,4-dione

5-Hydroxy-5-(3-methoxy-2-thienyl)-2,4,6(1H,3H,5H)-pyrimidinetrione (1 g.) was dissolved in 1N sodium hydroxide (20 ml.) and stirred for 1 hour. The mixture was acidified, clarified, extracted twice with 50 ml. portions of ethyl acetate. The combined ethyl acetate extracts were back-washed with water and evaporated to dryness (0.5 g. of solids). Chromatography on about 85 ml. of silica gel, monitored by tlc, afforded 5-(3-methoxy-2-thienyl)oxazolidine-2,4-dione (300 mg., m.p. 156-158°C.).

Analysis: Calcd. for $C_8H_7O_4NS$:

C, 45.08; H, 3.31; N, 6.57.

Found: C, 45.21; H, 3.39; N, 6.47.

EXAMPLE 1045-Hydroxy-5-(5-phenyl-2-furyl)-2,4,6(1H,3H,5H)-pyrimidinetrione

2-Phenylfuran (5.76 g., 40 mmoles) was combined with 100 ml. of tetrahydrofuran and cooled to -30°C. Butyl lithium in hexane (2.3M, 19.1 ml.) was added dropwise over 5 minutes, keeping the temperature between -20° and -30°C. The reaction mixture was allowed to warm to room temperature and then recooled to -30°C. Sublimed alloxan (5.96 g., 42 mmoles) in 40 ml. of tetrahydrofuran was added over 5 minutes, again keeping the temperature -20° to -30°C. The reaction mixture was again allowed to warm to room temperature, then recooled to 0°C. and 50 ml. of 1N hydrochloric acid added portionwise over 2-3 minutes. The quenched reaction mixture was extracted with 100 ml. of ethyl acetate. The extract was filtered through a bed of anhydrous magnesium sulfate, and evaporated to yield 5-hydroxy-5-(5-phenyl-2-furyl)-2,4,6(1H,3H,5H)pyrimidinetrione [9.4 g., gummy solid,

R_f 0.75 (1:1 hexane ethyl acetate/5% acetic acid)] contaminated with starting material (R_f 0.45).

EXAMPLE 105

5-(5-Phenyl-2-furyl)oxazolidine-2,4-dione

5 5-Hydroxy-5-(5-phenyl-2-furyl)-2,4,6(1H,3H,5H)-
pyrimidinetrione (0.7 g.) was dissolved in 15 ml. of
1N sodium hydroxide, stirred at room temperature for
15 minutes, extracted with ethyl acetate, made slightly
10 acidic with about 1 ml. of glacial acetic acid, and
extracted with 25 ml. of ethyl acetate. The latter
ethyl acetate extract was back washed with about
6.5 ml. of water, filtered over a bed of anhydrous
magnesium sulfate and evaporated to yield solid 5-(5-
phenyl-2-furyl)oxazolidine-2,4-dione [100 mg.; m.p.
15 216-218°C.; R_f 0.6 (1:1 hexane:ethyl acetate/5% acetic
acid)].

EXAMPLE 106

5-Hydroxy-5-(5-methyl-2-furyl)-
2,4,6(1H,3H,5H)pyrimidinetrione

20 2-Methylfuran (3.28 g., 3.58 ml., 40 mmoles) was
combined with 100 ml. of tetrahydrofuran. The reaction
mixture, flushed with nitrogen, was cooled to -30°C.
and butyl lithium (19.1 ml. of 2.3M in hexane) was
added over a period of 10 minutes, maintaining the
25 temperature at -20 to -30°C. The reaction mixture was
warmed to room temperature and then back to -30°C.
Sublimed alloxan (5.96 g.) in 40 ml. of tetrahydro-
furan was added dropwise over 10 minutes, keeping the
temperature at -20 to -30°C. The reaction mixture was
30 warmed to room temperature, cooled to 0°C. and 50 ml.
of 1N hydrochloric acid added portionwise, keeping the
temperature at 0 to 5°C. The reaction mixture was
extracted with 100 ml. of ethyl acetate. The extract
was back washed with 25 ml. of water, filtered through

a bed of anhydrous magnesium sulfate and evaporated to yield solid 5-hydroxy-5-(5-methyl-2-furyl)-2,4,6(1H,3H,5H)-pyrimidinetrione (6.3 g.; m/e 224).

EXAMPLE 107

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5-(5-Methyl-2-furyl)oxazolidine-2,4-dione

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5-Hydroxy-5-(5-methyl-2-furyl)-2,4,6(1H,3H,5H)-pyrimidinetrione (6.3 g.) was dissolved in 50 ml. of 1N sodium hydroxide and stirred at room temperature for 15 minutes. The reaction mixture was extracted with 50 ml. of ethyl acetate, and acidified with glacial acetic acid. Product was then extracted into fresh ethyl acetate (three 30 ml. portions). The combined ethyl acetate extracts were filtered through a bed of anhydrous magnesium sulfate and evaporated to an oil. The oil was chromatographed on 50 ml. of silica gel, with 1:1 hexane:ethyl acetate/5% acetic acid as eluant. The column was monitored by tlc using the same eluant. Clean product containing fractions were combined, evaporated to dryness and triturated with hexane (311 mg., m.p. 135-138°C.). Recrystallization from methanol/water afforded purified 5-(5-methyl-2-furyl)oxazolidine-2,4-dione (142 mg., m.p. 136.5-137.5°C.).

25

Analysis: Calcd. for $C_8H_7NO_4$:

C, 53.04; H, 3.90; N, 7.73.

Found: C, 52.82; H, 4.03; N, 7.65.

EXAMPLE 108

5-Hydroxy-5-(3-thienyl)-
2,4,6(1H,3H,5H)pyrimidinetrione

Isopropyl ether (40 ml.) was cooled to -70°C.

5 Butyl lithium in hexane (2.4M, 10 ml., 24 mmoles) was added over 10 minutes, keeping the temperature -70° to -60°C. 3-Bromothiophene (1.9 ml., 20 mmoles) was added over 20 minutes, keeping the temperature -72° to -68°C. The mixture was stirred for an additional 10 30 minutes at -72° to -70°C. Sublimed alloxan (3 g., 21 mmoles) in 25 ml. of tetrahydrofuran was added over 40 minutes, keeping the temperature -70° to -65°C. Stirring at this temperature was continued for 15 minutes. The cooling bath was removed and the reaction mixture 15 stirred for one hour at room temperature, then cooled to 5°C. Hydrochloric acid (1N, 40 ml.) was added slowly, and the organic phase separated. The aqueous phase was extracted with 35 ml. of ethyl acetate. The combined organic phase/extract was washed with 10 ml. 20 of water, dried over anhydrous sodium sulfate and concentrated to yield solid 5-hydroxy-5-(3-thienyl)-2,4,6(1H,3H,5H)pyrimidinetrione (1.41 g., 31%; m/e 226).

When this reaction was carried out in tetrahydro- 25 furan with reverse addition of the 3-bromothiophene to butyl lithium, with immediate addition of 0.5 equivalent of alloxan hydrate in place of 1 equivalent of anhydrous alloxan, the product was a mixture of the above trione and 5-(3-bromo-2-thienyl)-5-hydroxy-2,4,6(1H,3H,5H)- 30 pyrimidinetrione, which in turn was converted to a mixture of 5-(3-bromo-2-thienyl)oxazolidine-2,4-dione and 5-(3-thienyl)oxazolidine-2,4-dione by the method of Example 55.

EXAMPLE 1095-(3-Thienyl)oxazolidine-2,4-dione

5-Hydroxy-5-(3-thienyl)-2,4,6(1H,3H,5H)pyrimidine-trione (1.16 g., 5.1 mmoles) was dissolved in 1N sodium hydroxide (11 ml., 11 mmoles) and allowed to stand at room temperature for 15 minutes. The solution was acidified with acetic acid, and product allowed to crystallize over 35 minutes. Filtration gave 5-(3-thienyl)oxazolidine-2,4-dione (480 mg., 51%; m.p. 133-135°C.). An additional crop of product was obtained by extracting the mother liquor with ethyl acetate. The extract was back washed with water, and evaporated to dryness (80 mg., contaminated with starting material).

EXAMPLE 1105-(3-Furyl)-5-hydroxy-2,4,6(1H,3H,5H)pyrimidinetrione

The detailed procedure of Example 108, but substituting 3-bromofuran (2.94 g., 1.8 ml., 20 mmoles) for the 3-bromothiophene, was employed to produce 5-(3-furyl)-5-hydroxy-2,4,6(1H,3H,5H)pyrimidinetrione (1.62 g., oil, m/e 210).

EXAMPLE 1115-(3-Furyl)oxazolidine-2,4-dione

5-(3-Furyl)-5-hydroxy-2,4,6(1H,3H,5H)pyrimidine-trione (1.62 g.) was dissolved in 15 ml. of 1N sodium hydroxide, and allowed to stand for 15 minutes at room temperature, and then extracted with 5 ml. of ethyl acetate. The aqueous layer was acidified with glacial acetic acid (about 1.5 ml.) and product extracted into 25 ml. of ethyl acetate. The extract was back washed with 5 ml. of water, filtered through a bed of anhydrous sodium sulfate, and evaporated to yield crude product as an oil (470 mg., m/e 167). Crystallization from chloroform gave purified 5-(3-furyl)oxazolidine-2,4-dione (129 mg., m.p. 88-90°C., m/e 167). A second, lower melting crop was obtained from mother liquor.

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EXAMPLE 112

3-Thenaldehyde Cyanohydrin

Sodium bisulfite (30.2 g., 0.29 mole) was dissolved in 190 ml. of water and warmed to 50°C. 3-Thenaldehyde (25 g., 0.22 mole) was added and the reaction mixture held at 50-55°C. for 35 minutes, by which time all but a small amount of gummy solids were in solution. The mixture was cooled to 5°C. and layered with 190 ml. of isopropyl ether. With stirring, sodium cyanide (24.8 g., 0.25 mole) in 190 ml. of water was added dropwise over 20 minutes, keeping the temperature below 10°C. Stirring was continued at room temperature for 1 hour. The organic layer was separated, and the aqueous phase extracted with fresh isopropyl ether (300 ml.). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to yield 3-thenaldehyde cyanohydrin as an oil (28.3 g., 92%).

EXAMPLE 113

2-Hydroxy-2-(3-thienyl)acetamide

Formic acid (0.5 ml.) was cooled in an ice-water bath. 3-Thenaldehyde cyanohydrin (1.0 g.) and then concentrated hydrochloric acid (0.5 ml.) were added. The reaction mixture was stirred at room temperature for 1 hour, poured over crushed ice, and extracted with three portions of ethyl acetate. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to an oil, which partially crystallized on scratching. Recrystallization from ethyl acetate gave 2-hydroxy-2-(3-thienyl)acetamide (389 mg., 35%, m.p. 123-126°C., m/e 157).

EXAMPLE 114

Mixed Methyl/Ethyl Esters of
2-Benzoyl-2-(3-thienyl)malonic Acid

Commercially available mixed esters of 2-(3-thienyl)malonic acid (47% diethyl, 43% methyl/ethyl, 10% dimethyl; 11.4 g.) were added portionwise to a dispersion of sodium hydride in oil (50%, 2.4 g.) slurried in 70 ml. of toluene. An exotherm was noted, the temperature rising to 45°C. The reaction mixture was stirred for 3 hours at room temperature, and then cooled in an ice-water bath. Benzoyl peroxide (8 g.) in 100 ml. of toluene was added over a period of 1 hour, maintaining the temperature 10-20°C. The mixture was stirred for 30 minutes at room temperature, diluted dropwise with 50 ml. of water (initial foaming noted), and finally diluted with 50 ml. of ether. The organic phase was separated, back washed with three 25 ml. portions of water, and evaporated to yield mixed methyl/ethyl esters of 2-benzoyloxy-2-(3-thienyl)-malonic acid as an oil (15.5 g. containing about 1.2 g. of oil from the sodium hydride dispersion).

EXAMPLE 1155-(3-Thienyl)oxazolidine-2,4-dione

Sodium (0.46 g., 20 mmoles) was dissolved in 50 ml. of absolute ethanol. To the resulting warm solution of sodium ethoxide (about 60°C.), crude mixed esters of 2-benzoyloxy-2-(3-thienyl)malonic acid (7 g., approximately 20 mmoles, as prepared in Example 60) were added, followed by urea (1.2 g., 20 mmoles) dissolved in 20 ml. of hot ethanol. The reaction mixture was heated in an oil bath at 105-110°C. for 4.5 hours. The reaction mixture was cooled, acidified with concentrated hydrochloric acid, and extracted with ethyl acetate. The extract was back washed with water and concentrated to an oil. Trituration with 20 ml. of 1:1 ether:hexane gave a mixture of 5-(3-thienyl)oxazolidine-2,4-dione and intermediate 5-benzoyloxy-5-(3-thienyl)2,4,6(1H,3H,5H)pyrimidinetrione (0.8 g.). A portion of this mixture (0.3 g.) was dissolved in 1N sodium hydroxide (5 ml.) and allowed to stand for 20 minutes at room temperature. The reaction mixture was clarified by filtration, and acidified with acetic acid to precipitate 5-(3-thienyl)-oxazolidine-2,4-dione (100 mg., m.p. 136-138°C.).

EXAMPLE 116

2-(3-Benzo[b]thienyl)-2-trimethylsiloxyethanenitrile

5 Benzo[b]thiophene-3-carbaldehyde [1.8 g., 11 mmoles,
J. Chem. Soc. C., pp. 339-340 (1969)] and about 100 mg.
of zinc iodide were combined in 35 ml. of ether.
Trimethylsilylcarbonitrile (1.98 g., 20 mmoles) was
added dropwise. After approximately 1 hour, the
10 reaction mixture was washed in sequence with saturated
sodium bicarbonate, water and brine, dried over
anhydrous sodium sulfate, filtered and evaporated to
yield 2-(3-benzo[b]thienyl)-2-trimethylsiloxyethane-
nitrile [2.5 g., oil, R_f 0.7 (1:2 ethyl acetate:hexane)].

EXAMPLE-117

15 Ethyl 1-(3-Benzo[b]thienyl)-1-hydroxymethanecarboximidate Hydrochloride

With cooling in an ice-water bath, 2-(3-benzo[b]-
thienyl)-2-trimethylsiloxyethanenitrile (2.3 g.) was
dissolved in 10 ml. of saturated ethanolic hydrogen
20 chloride, and held for 16 hours at about 5°C. The
reaction mixture was evaporated to dryness and triturated
with ether to yield 1-(3-benzo[b]thienyl)-1-hydroxy-
methanecarboximidate hydrochloride (2.2 g., m.p.
128-131°C., m/e 235).

EXAMPLE 1185-(3-Benzo[b]thienyl)oxazolidine-2,4-dione

Ethyl 1-(3-benzo[b]thienyl)-1-hydroxymethane-carboximidate hydrochloride (2.36 g., 8.7 mmoles) and triethylamine (2.64 g., 26 mmoles) were combined in 50 ml. of tetrahydrofuran and cooled to 10°C. Phosgene was bubbled through the cooled reaction mixture for 30 minutes, followed by a 10 minute flush with nitrogen. The reaction mixture was slowly poured into 100 ml. of ice and extracted twice with ether. The combined ether extracts were back-washed with water and then brine, dried over anhydrous sodium sulfate, filtered, and evaporated to yield a gummy solid (1.7 g.). This crude product was dissolved in 1N sodium hydroxide, washed twice with ether and acidified with 6N hydrochloric acid, affording purified 5-(3-benzo[b]thienyl)-oxazolidine-2,4-dione (950 mg., m.p. 202-205°C., m/e 233).

Analysis: Calcd. for $C_{11}H_7O_3NS$:

C, 56.64; H, 3.02; N, 6.00.

Found: C, 56.74; H, 3.18; N, 5.69.

EXAMPLE 119

2-(7-Benzo[b]thienyl)-2-
trimethylsiloxyethanenitrile

Benzo[b]thiophene-7-carbaldehyde [1.3 g., 8 mmoles, J. Org. Chem. 39, 2829 (1974)] was dissolved in 35 ml. of ether. Trimethylsilylcarbonitrile (1.5 ml., 12 mmoles) and zinc iodide (about 50 mg.) were added and the mixture stirred for 1 hour at room temperature, at which time tlc indicated conversion was complete. The reaction mixture was evaporated to dryness, yielding 2-(7-benzo[b]thienyl)-2-trimethylsiloxyethanenitrile [2.2 g., oil; R_f 0.6 (1:5 ethyl acetate:hexane/5% acetic acid)].

EXAMPLE 120

Ethyl 1-(7-Benzo[b]thienyl)-1-
hydroxymethanecarboximate Hydrochloride

By the procedure of Example 112, 2-(7-benzo[b]-
thienyl)-2-trimethylsiloxyethanenitrile (2.1 g.),
using 35 ml. of saturated ethanolic hydrogen chloride,
was converted to ethyl 1-(7-benzo[b]thienyl-1-hydroxy-
methanecarboximate hydrochloride (1.1 g., m.p.
120-122°C.), after crystallization from acetone.

EXAMPLE 121

5-(7-Benzo[b]thienyl)oxazolidine-2,4-dione

Following the procedure of Example 118, ethyl 1-
(7-benzo[b]thienyl)-1-hydroxymethanecarboximate
hydrochloride (1.1 g., 4 mmoles) and triethylamine
(1.7 ml., 12 mmoles) were reacted with phosgene. The
crude product, isolated as an oil, was dissolved in
25 ml. ether and product extracted into 50 ml. of 1N
sodium hydroxide. This aqueous extract was acidified
with concentrated hydrochloric acid and product
extracted into fresh ether, which was back washed with
water and evaporated in vacuo to a solid residue
(670 mg.). This residue was recrystallized to yield
5-(7-benzo[b]thienyl)oxazolidine-2,4-dione (0.45 g.,
m.p. 130-132°C.).

Analysis: Calcd. for $C_{11}H_7O_3NS$:

C, 56.64; H, 3.02; N, 6.00.

Found: C, 56.42; H, 3.18; N, 5.91.

EXAMPLE 1225-Hydroxy-5-(5-methoxy-2-thienyl)-
2,4,6(1H,3H,5H)-pyrimidinetrione

- 2-Methoxythiophene (2.3 g., 20 mmoles) was dissolved in 35 ml. of ether. With cooling, butyllithium in hexane (2.4M, 9 ml., 21.6 mmoles) was added dropwise over 15 minutes, the temperature rising as high as 35°C. during this addition. The reaction mixture was stirred for 1 hour at room temperature.
- While maintaining the temperature between -20° and -15°C., sublimed alloxan (3 g., 21 mmoles) in 20 ml. of tetrahydrofuran was added during 10 minutes. The mixture was warmed to room temperature, stirred for 0.5 hour, cooled to 5°C. and quenched by adding 35 ml. of 1N hydrochloric acid in portions. The organic phase was separated and the aqueous phase extracted with 25 ml. of ethyl acetate. The combined organic phase and extract were back-washed with water, concentrated to dryness and triturated with hexane to yield solid 5-hydroxy-5-(5-methoxy-2-thienyl)-2,4,6(1H,3H,5H)-pyrimidinetrione (1.4 g., m/e 256).

EXAMPLE 1235-(5-Methoxy-2-thienyl)oxazolidine-2,4-dione

- 5-Hydroxy-5-(5-methoxy-2-thienyl)-2,4,6(1H,3H,5H)-pyrimidinetrione (1.1 g.) was dissolved in 10 ml. of 1N sodium hydroxide, allowed to stand for 1.5 hours at room temperature, extracted with ether, acidified with acetic acid, diluted with 15 ml. of water and filtered to yield product [567 mg., m.p. 144-146°C. (dec.)].
- Recrystallization from acetone-hexane gave purified 5-(5-methoxy-2-thienyl)oxazolidine-2,4-dione in two crops [487 mg., m.p. 147-148°C. (dec.)].

Analysis: Calcd. for $C_8H_7O_4NS$:

C, 45.08; H, 3.31; N, 6.57.

- Found: C, 45.08; H, 3.41; N, 6.39.

EXAMPLE 124

5-[5-(2-phenyl-1,3-dioxolan-2-yl)-2-thienyl]-2,4,6(1H,3H,5H)-pyrimidinetrione

At room temperature, 2-phenyl-2-thienyl)-1,3-dioxolane (3.26 g., 14 mmoles) was dissolved in 35 ml. of ether. Butyl lithium in hexane (2.4M, 6.25 ml., 15 mmoles) was added dropwise over 15 minutes, the temperature rising to 33°C. The mixture was stirred for 75 minutes at room temperature and then cooled. Maintaining the temperature between -15° and -20°C., sublimed alloxan (2.13 g., 15 mmoles) in 20 ml. of tetrahydrofuran was added dropwise over 10 minutes. The reaction mixture was stirred at room temperature for 30 minutes, cooled to 5°C., quenched with 35 ml. of 1N hydrochloric acid, added in small portions, and extracted with 25 ml. of ethyl acetate. The organic layer was back washed with 15 ml. of water, filtered through a bed of anhydrous sodium sulfate, and evaporated to yield 5-[5-(2-phenyl-1,3-dioxolan-2-yl)thienyl]-2,4,6(1H,3H,5H)-pyrimidinetrione [oil, R_f 0.25 (1:1 hexane:ethyl acetate/5% acetic acid)] contaminated with starting material (R_f 0.8).

EXAMPLE 125

5-[5-(2-Phenyl-1,3-dioxolan-2-yl)-2-thienyl]oxazolidine-2,4-dione

The entire crude product from the preceding Example was taken into 35 ml. of 1N sodium hydroxide and allowed to stand for 30 minutes. After acidification the product was extracted into isopropyl ether. The extract was back washed with water and evaporated to yield 5-[5-(2-phenyl-1,3-dioxolan-2-yl)thienyl]-oxazolidine-2,4-dione [0.40 g., R_f 0.65 (1:1 ethyl acetate:hexane/5% acetic acid)].

EXAMPLE 1265-(5-Benzoyl-2-thienyl)oxazolidine-2,4-dione

5-[5-(2-Phenyl-1,3-dioxolan-2-yl)-2-thienyl]-oxazolidine-2,4-dione (0.40 g.) was dissolved in 30 ml. of ether and stirred with 10 ml. of 6N hydrochloric acid at room temperature for 1 hour. Ethyl acetate (10 ml.) was added, and the organic layer was separated and evaporated in vacuo to dryness (0.388 g.). Chromatography on 50 ml. of silica gel, eluted with 1:1 hexane:ethyl acetate/5% acetic acid and monitored by tlc, gave in early fractions purified 5-(5-benzoyl-2-thienyl)oxazolidine-2,4-dione (0.22 g., m.p. 153-155°C., m/e 287).

Analysis: Calcd. for $C_{14}H_9O_4NS$: -

C, 58.52; H, 3.16; N, 4.87.

Found: C, 58.69; H, 3.50; N, 4.94.

EXAMPLE 1275-(3-Thienyl)oxazolidine-2,4-dione Capsules

The following ingredients were combined and blended for 30 minutes:

Sodium 5-(3-thienyl)oxazolidine-2,4-dione monohydrate	30.46*
Lactose, anhydrous, U.S.P.	14.05 g.
Corn starch, dried, U.S.P.	5.00 g.
*Equivalent to 25 g. of active drug (unsolvated free acid).	

The mixture was milled (0.040 inch plate) and blended for an additional 30 minutes. Magnesium stearate, sodium lauryl sulfate, 90/10 blend (1.00 g.) was added and the mixture blended for 20 minutes. The blend was filled into #0 gelatin capsules (505 mg. fill weight) so as to obtain capsules of 250 mg. potency.

Larger capsules are employed to prepare capsules of higher potency.

The same procedure was employed to prepare capsules of 100 mg. potency from the following ingredients:

Sodium 5-(3-thienyl)oxazolidine-2,4-dione monohydrate	12.18 g.*
Lactose, anhydrous, U.S.P.	32.32 g.
Corn starch, dried, U.S.P.	5.00 g.
Magnesium stearate/lauryl sulfate (90/10 blend)	0.50 g.

*Equivalent to 10 g. of activated ingredient (unsolvated free acid).

A lower level of active ingredient in the blend is used to prepare capsules of lower potency.

EXAMPLE 128

Tablets

A tablet base is prepared by blending the following ingredients in the proportion by weight indicated:

Sucrose, U.S.P.	80.3
Tapioca starch	13.2
Magnesium stearate	6.5

Into this tablet base there is blended sufficient sodium 5-(3-thienyl)oxazolidine-2,4-dione monohydrate to form tablets containing 50 mg., 100 mg. or 250 mg. of active drug (weight equivalent to the free acid). The portion of blend to active drug is within the limits of 1-0.167 to 1-1, e.g., in the extremes, 60.2 mg. of sodium salt monohydrate and 300 mg. of blend in a 50 mg. tablet or 304.6 mg. of sodium salt monohydrate and 250 mg. of blend in a 250 mg. tablet.

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EXAMPLE 129

Injectable Preparation

Sterile sodium 5-(3-thienyl)oxazolidine-2,4-dione is dry filled into vials so as to contain 670.1 mg. of the sodium salt monohydrate per vial (equivalent to 550 mg. of free acid). Prior to use, sterile water for injection (11 ml.) is added, and the mixture shaken to form a solution, containing 50 mg./ml. of active drug, which is suitable for intravenous, intramuscular or subcutaneous injection.

Alternatively vials are filled by a freeze drying procedure. Two ml. of a sterile, aqueous solution containing 335 mg./ml. of sodium salt monohydrate is introduced into each vial. The vials are freeze dried on trays.

EXAMPLE 130

3-Ethoxycarbonyl-5-(3-thienyl)oxazolidine-2,4-dione

Sodium 5-(3-thienyl)oxazolidine-2,4-dione monohydrate is stripped of water by drying in vacuo at elevated temperature (50-70°C.). The anhydrous salt (2.05 g., 10 mmoles) is suspended in 35 ml. of 1,2-dichloroethane. Ethyl chloroformate (1.41 g., 10 mmoles) is added and the mixture refluxed for about 2 hours. The reaction mixture is cooled to room temperature, by-product sodium chloride removed by filtration and the filtrate concentrated to dryness to yield 3-ethoxycarbonyl-5-(3-thienyl)oxazolidin-2,4-dione.

Substitution of the ethyl chloroformate with an equivalent quantity of acetyl chloride, isobutyryl chloride, N,N-dimethylcarbamoyl chloride, or benzoyl chloride produces, respectively, 3-acetyl-5-(3-thienyl)oxazolidine-2,4-dione, 3-isobutyryl-5-(3-thienyl)oxazolidine-2,4-dione, 3-(N,N-dimethylcarbamoyl)-5-(3-thienyl)oxazolidine-2,4-dione and 3-benzoyl-5-(3-thienyl)oxazolidine-2,4-dione.

EXAMPLE 1313-Acetyl-5-(3-thienyl)oxazolidine-2,4-dioneMethod A

5 5-(3-Thienyl)oxazolidine-2,4-dione (1.83 g.,
10 mmoles) and triethylamine (0.14 ml., 10 mmoles) are
combined with 25 ml. of 1,2-dichloroethane at room
temperature. Acetyl chloride (0.72 ml., 10 mmoles) is
added dropwise over a few minutes and the reaction
mixture stirred for 3 hours. The reaction mixture is
10 evaporated to dryness and the residue distributed
between saturated sodium bicarbonate and chloroform.
The chloroform layer is washed with water, and then
brine, dried over anhydrous magnesium sulfate, filter-
ed and evaporated to yield 3-acetyl-5-(3-thienyl)-
15 oxazolidine-2,4-dione.

Method B

5-(3-Thienyl)oxazolidine-2,4-dione (1.83 g.,
10 mmoles) and acetic anhydride (1.14 ml., 12 mmoles)
are combined with 20 ml. of tetrahydrofuran and
20 stirred for 40 hours. The reaction mixture is evaporated
to dryness and 3-acetyl-5-(3-thienyl)oxazolidine-2,4-
dione further isolated as in Method A.

The same procedure, but substituting acetic
anhydride with an equivalent of acetoformic acid
25 reagent [a solution of acetic-formic anhydride in
acetic acid; cf. Blackwood et al., J. Am. Chem. Soc.,
82, 5194 (1960)], propionic anhydride or benzoic
anhydride, allows formation of corresponding 3-formyl-
5-(3-thienyl)oxazolidine-2,4-dione, 3-propionyl-5-(3-
30 thienyl)oxazolidine-2,4-dione and 3-benzoyl-5-(3-
thienyl)oxazolidine-2,4-dione.

EXAMPLE 132

3-(N-Methylcarbamoyl)-5-
(3-thienyl)oxazolidine-2,4-dione

5 5-(3-Thienyl)oxazolidine-2,4-dione (1.83 g.,
10 moles) and one drop of triethylamine are combined
in 35 ml. of 1,2-dichloroethane. Methyl isocyanate
(0.58 ml., 10 mmoles) is then added and the reaction
mixture stirred for 4 hours at room temperature. The
reaction is diluted with 35 ml. of 1,2-dichloroethane,
10 washed with saturated sodium bicarbonate and then
brine, dried over magnesium sulfate, filtered and
concentrated to yield 3-(N-methyl)-5-(3-thienyl)-
oxazolidine-2,4-dione.

EXAMPLE 1333-(4-Methoxy-3-thienyl)-2-trimethylsiloxyethanenitrile

By the procedure of Example 55, 4-methoxy-3-thenaldehyde (2.6 g., 18.3 mmole) and trimethylsilyl-carbonitrile (2.15 g., 21.7 mmole) in 250 ml. of ether in the presence of 50 mg. of zinc iodide was converted to title product as an oil (3.9 g., m/e 241).

EXAMPLE 134

Methyl 1-Hydroxy-1-(4-methoxy-3-thienyl)
methanecarboximidate Hydrochloride

10

Saturated methanolic hydrogen chloride (100 ml.) was maintained at 0-5°C. in an ice bath. Title product of the preceding Example (3.9 g.) in 20 ml. of methanol was added dropwise and the mixture held for 1 hour at 0-5°C. The reaction mixture was concentrated to solids and the residue triturated with ether to yield the title product [2.76 g., m.p. 94-99°C. (dec.)]. Recrystallization from methanol-ether gave purified title product [1.51 g.; m.p. 112-114 (dec.); m/e 201].

20

EXAMPLE 1355-(4-Methoxy-3-thienyl)oxazolidine-2,4-dione

By the procedure of Example 57, the product of the preceding Example (1.3 g., 5.5 mmoles) and triethylamine (1.7 g., 17 mmoles) in 50 ml. of tetrahydrofuran were reacted with phosgene for 30 minutes at 0-5°C. The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured slowly into 500 ml. of crushed ice and extracted with three 50 ml. portions of chloroform. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to solids. Recrystallization from toluene gave purified title product [510 mg.; m.p. 120-222°C.; ir (KBr) 1377, 1732, 1767, 1808 cm⁻¹].

30

Analysis: Calcd. for C₈H₇O₄NS:

35

C, 45.06; H, 3.31; N, 6.57.

Found: C, 45.31; H, 3.41; N, 6.85.

EXAMPLE 1363-(4-Ethoxy-3-thienyl)-2-trimethylsiloxymethanenitrile

By the procedure of Example 55, 4-ethoxy-3-thienaldehyde (8.1 g., 0.052 mole) and trimethylsilylcarbo-
nitrile (6.13 g., 0.062 mole) in 300 ml. of ether, in
the presence of 50 mg. of zinc iodide, were converted
to title product (13 g.) as a viscous oil; pmr
indicated absence of the aldehyde proton.

EXAMPLE 137Ethyl 1-Hydroxy-1-(4-ethoxy-3-thienyl)-
methanecarboximidate Hydrochloride

Using ethanol in place of methanol, but otherwise
the procedure of Example 134, product of the preceding
Example (13 g.) was converted to title compound
[9.23 g., m.p. 126-128° (dec.)].

EXAMPLE 1385-(4-Ethoxy-2-thienyl)oxazolidine-2,4-dione

Using a phosgene perfusion time of 1 hour at
0-5°C. and a further reaction time of 1 hour at room
temperature, product of the preceding Example (9.2 g.)
was converted to title product. To isolate the product,
the reaction was poured in 1.5 l. of crushed ice and
extracted with three 200 ml. portions of chloroform.
The organic layers were combined and extracted with
three 150 ml. portions of 1N sodium hydroxide. The
basic extracts were combined, back-washed with 200 ml.
of fresh chloroform, reacidified with 3N hydrochloric
acid and extracted with three 200 ml. portions of
chloroform. The last three organic extracts were
combined, washed with brine, dried over magnesium
sulfate, filtered, evaporated to solids, and the
residue crystallized from toluene to yield title
compound [4.06 g., m.p. 144-146°C., m/e 227; ir (KBr)
1822, 1737, 1568 cm⁻¹].

Analysis: Calcd. for $C_9H_9O_4NS$:

C, 47.57; H, 3.99; N, 6.17

Found: C, 47.18; H, 4.04; N, 6.06.

5 The chloroform back-wash was reextracted with three 150 ml. portions of fresh 1N sodium hydroxide. These basic extracts were combined and additional product (980 mg., m.p. 144-146°C.) recovered in like manner.

EXAMPLE 139

10 2-[4-(n-Propoxy)-3-thienyl]-2-
trimethylsiloxyethanenitrile

By the procedure of Example 55, 4-(n-propoxy)-3-thenaldehyde (3.1 g., 18 mmoles) and trimethylsilyl-carbonitrile (2.28 g., 2.9 ml., 23 mmoles) in 250 ml. of ether, in the presence of 50 mg. of zinc iodide,
15 were converted to title product as an oil [4.6 g.; m/e 269; ir (CH_2Cl_2) 2936, 1558 cm^{-1}].

EXAMPLE 140

Ethyl 1-Hydroxy-1-[4-(n-propoxy)-
3-thienyl]methanecarboximidate Hydrochloride

20 Using a reaction time of 20 minutes after completion of the addition, the procedure of Example 137 was used to convert the product of the preceding Example (4.5 g.) into title product of the present Example [3.05 g., m.p. 127-129°C. (dec.)].

25 EXAMPLE 141

5-[4-(n-Propoxy)-3-thienyl]-
oxazolidine-2,4-dione

By the procedure of Example 135, the product of the preceding Example (2.8 g., 0.01 mole) was converted
30 to toluene recrystallized 5-[4-(n-propoxy)-3-thienyl]-oxazolidine-2,4-dione [1.63 g.; m.p. 134-136°C.; m/e 241; ir (KBr) 1827, 1747, 1564 cm^{-1}].

EXAMPLE 1422-(4-Methoxy-2-methyl-3-thienyl)-
2-trimethylsiloxyethanenitrile

By the procedure of Example 55, 4-methoxy-2-methyl-3-thienaldehyde (5.2 g., 33.3 mmoles) and trimethylsilylcarbonitrile (3.96 g., 40 mmoles) in 350 ml. of ether, in the presence of 50 mg. of zinc iodide, were converted to title product, isolated as a viscous oil [7.3 g.; m/e 255; ir (CH_2Cl_2) 1575, 1204, 1075 cm^{-1}].

EXAMPLE 143Ethyl 1-Hydroxy-1-(4-methoxy-2-methyl-3-thienyl)methanecarboximidate Hydrochloride

The procedure of Example 137 was applied to the product of the preceding Example (7.2 g.) to produce 5.8 g. of a mixture of title compound and the corresponding ethoxy ether (estimated by pmr to be about 40% methyl ether and 60% ethyl ether; showing both m/e 243 and 229).

A portion of this mixture (2.5 g.) was taken into 100 ml. of methanol, cooled to 0-5°C., and perfused with hydrogen chloride for 1 hour. After 1 hour additional stirring at 0°C., the reaction mixture was evaporated to a viscous oil. Crystallization from ether gave title product [2.1 g.; m.p. 123-125°C. (dec.); m/e 229].

The corresponding methyl imidate ester of the title product is obtained by directly reacting the product of the preceding Example with methanolic hydrogen chloride according to the procedure of Example 134.

EXAMPLE 144Ethyl 1-(Hydroxy)-1-(4-Ethoxy-2-methyl-3-thienyl)methanecarboximidate Hydrochloride

5 A portion of the mixed methyl and ethyl ethers of the preceding Example (2.5 g.) was taken into 100 ml. of ethanol and cooled to 0°C. The cold solution was perfused with hydrogen chloride for 1 hour, stirred for an additional hour at 0°C. and evaporated to an oil. The oil was crystallized by trituration with
10 ether. Repulping in ether gave title product [2.07 g., m.p. 105-107°C. (dec.); m/e 243].

EXAMPLE 1455-(4-Methoxy-2-methyl-3-thienyl)oxazolidine-2,4-dione

15 Using a reaction time of 3.5 hours at room temperature, but otherwise following the procedure of Example 57, the product of Example 143 (2.0 g., 7.5 mmoles) was converted to toluene recrystallized title product [0.52 g., m.p. 179-181°C.; m/e 227; ir (KBr) 1820, 1750, 1727, 1583 cm⁻¹].

EXAMPLE 1465-(4-Ethoxy-2-methyl-3-thienyl)oxazolidine-2,4-dione

20 By the procedure of the preceding Example, the product of Example 144 (1.9 g.) was converted to title product [245 mg., m.p. 136-138°C.; m/e 241; ir (KBr)
25 1824, 1743 cm⁻¹].

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EXAMPLE 147

5-Hydroxy-(2,5-Dimethyl-3-furyl)-
2,4,6(1H,3H,5H)pyrimidinetrione

Isopropyl ether (35 ml.) was cooled to -68°C.

5 Butyl lithium (5 ml. of 2.1M in hexane, 10.5 mmoles) was added, allowing the temperature to rise to -60°C. 2,5-Dimethyl-3-iodofuran [J. Am. Chem. Soc. 70, p. 739 (1948); 1.2 ml, 9 mmoles] was then added dropwise keeping the temperature between -65 and -68°C. After

10 stirring for 0.5 hour at -68°C., anhydrous alloxan (1.5 g., 10.6 mmoles) dissolved in 15 ml. of tetrahydrofuran was added dropwise over 30 minutes, keeping the temperature -65 to -60°C. The stirred reaction mixture was warmed over 15 minutes to 0°C., 1N hydro-

15 chloric acid (25 ml.) was added and the organic phase separated. The aqueous phase was extracted with 20 ml. of ethyl acetate. The combined organic layers were washed with 10 ml. of water and evaporated to yield title product (1 g., R_f 0.05 (1:5 ethyl acetate:

20 hexane/5% acetic acid)].

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EXAMPLE 1485-(2,5-Dimethyl-3-furyl)oxazolidine-2,4-dione

Product of the preceding Example (1 g.) was taken into 10 ml. of 1N sodium hydroxide and held for 15 minutes. The solution was extracted with 5 ml. of ethyl acetate, acidified with acetic acid and extracted with 25 ml. of ethyl acetate. The acidic extract was back-washed with 5 ml. of water and evaporated to solids (340 mg.), which were chromatographed on 50 ml. of silica gel, using 1:1 ethyl acetate:hexane as eluant and tlc monitoring. Clean fractions were combined, evaporated to dryness and the residue recrystallized from ether-hexane to yield purified title product [170 mg.; m.p. 144-145°; m/e 195; R_f 0.3 (1:5 ethyl acetate:hexane/5% acetic acid); R_f 0.55 (1:1 ethyl acetate:hexane)].

Analysis: Calcd. for $C_9H_9O_4N$:

C, 55.38; H, 4.65; N, 7.18

Found: C, 55.15; H, 4.76; N, 7.04.

EXAMPLE 1495-Hydroxy-5-(4-iodo-3-furyl)-
2,4,6(1H,3H,5H)pyrimidinetrione

3,4-Diiodofuran (0.96 g., 3 mmoles) in 5 ml. of ether was added slowly to a cold (-65°C.) solution of butyl lithium (2 ml. of 2.3M in hexane, 4.6 mmoles) in 15 ml. of ether. The mixture was stirred for 20 minutes at -65°C. Anhydrous alloxan (0.57 g., 4 mmoles) was dissolved in 10 ml. of tetrahydrofuran and added slowly to the 4-iodo-3-furyl lithium solution at -65°C. After 10 minutes at the same temperature, the reaction mixture was warmed to 15°C., acidified with 15 ml. of 1N hydrochloric acid and extracted with ether. The ether extract was back-washed with 10 ml. of water, concentrated to dryness and the residue triturated with 2 ml. of hexane to yield title product [108 mg.; m/e 336; R_f 0.5 (1:1 ethyl acetate:hexane/5% acetic acid)].

EXAMPLE 150

5-(4-Iodo-3-furyl)oxazolidine-2,4-dione

Product of the preceding Example (100 mg.) was allowed to stand with 1 ml. of 1N sodium hydroxide for 15 minutes at room temperature. The reaction mixture was acidified with acetic acid and extracted with 3 ml. of ethyl acetate. The organic extract was back-washed with 1 ml. of water and evaporated to a gum (63 mg.). Crude material (120 mg.) prepared in this manner was chromatographed on 50 ml. of silica gel using 1:1 ethyl acetate:hexane as eluant and tlc monitoring. The first fractions from the column were combined and evaporated to a gum (78 mg. which crystallized from chloroform to yield purified title product (45 mg.; m.p. 140-144°C.).

Analysis: Calcd. for $C_7H_4O_4NI$:

C, 28.69; H, 1.38; N, 4.78

Found: C, 28.37; H, 1.62; N, 4.74.

EXAMPLE 151

5-(5-Chloro-7-benzo[b]furanyl)oxazolidine-2,4-dione

Title product of Example 50 (100 mg., 0.39 mmole) was suspended in 6 ml. of chloroform and bis(trimethylsilyl)trifluoroacetamide (100 mg., 0.104 ml., 0.39 mmole) added in one portion. After stirring for 1 minute, N-bromosuccinimide (69 mg., 0.39 mmole) was added together with a trace (a single crystal) of benzoyl peroxide. The mixture was heated to reflux for 2 hours, cooled to room temperature, filtered from insolubles and evaporated to semisolids under a stream of nitrogen. The residue was partitioned between 1N sodium hydroxide and ethyl acetate. The aqueous layer was separated, washed with fresh ethyl acetate, acidified with 1N hydrochloric acid and extracted with three portions of chloroform. The chloroform extracts were combined, dried over anhydrous magnesium sulfate, filtered, concentrated to an oil, and title product crystallized from toluene (44 mg.; m.p. 154-157°C.; m/e 251.253).

By the same method the fluoro analog of Example 50 is converted to 5-(5-fluoro-7-benzo[b]furanyl)oxazolidine-2,4-dione.

PREPARATION 12-Ethoxy-3-pyridinecarboxylic Acid

Sodium ethoxide was prepared by adding sodium (1.4 g., 0.06 mole) portion wise to 50 ml. of anhydrous ethanol. The solution was diluted with 20 ml. of ethanol and 4.5 g. of 2-chloropyridine-3-carboxylic was added. The reaction mixture was heated in a steel pressure vessel at 170°C. for 6 hours. The vessel was cooled and the contents evaporated to dryness in vacuo. The residue was taken up in 150 ml. of water and acidified to constant pH 4.5. The water solution was saturated with salt and extracted with four portions of ethyl acetate. The combined ethyl acetate layers were back washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated to yield title product (4.33 g., m.p. 85-88°C.).

PREPARATION 22-Methoxy-3-pyridinecarboxylic Acid

A stainless steel stirred autoclave was charged sequentially with methanol (2.8 l.), sodium methoxide (259 g.) (in portions, keeping the temperature less than 35°C.), and 2-chloro-3-pyridinecarboxylic acid (190 g.). The autoclave was sealed and the reaction mixture heated at 110°C. (50 psig) for 48 hours. The reaction mixture was cooled to 25°C. and discharged from the autoclave. Solids were recovered by filtration. Concentration of the filtrate gave a second crop. These process steps were repeated until virtually all of the methanol had been removed. The several crops of solids were combined, taken up in 2.5 liters of water and acidified with conc. hydrochloric acid to pH 2.7 keeping the temperature below 20°C. The precipitated product was granulated for 30 minutes at 15°C. and recovered by filtration (141 g.). Purified title product was obtained by recrystallization from ethyl acetate-hexane (120.5 g., m.p. 148-150°C.).

PREPARATION 3Ethyl 2-(6-Chloro-8-quinolyl)-2-oxoacetate

8-Bromo-6-chloroquinoline [J. Het. Chem. 6, pp. 243-245 (1969); 6 g., 0.025 mole] in 50 ml. of tetrahydrofuran was added dropwise over a 10 minute period to a mixture of butyl lithium (2.3M in hexane, 12.2 ml., 0.028 mole) and 40 ml. of tetrahydrofuran held at -70°C. After an additional 30 minutes at this temperature, a cold (0°C.) solution of diethyl oxalate (14.6 g., 0.10 mole) in 50 ml. of tetrahydrofuran was added dropwise. The reaction mixture was maintained at 0°C. for 1 hour, then quenched at 0-5°C. with glacial acetic acid (17 ml.) in 50 ml. of tetrahydrofuran. After warming to room temperature-the quenched mixture was poured into 500 ml. of water and then diluted with 500 ml. of ethyl acetate and 500 ml. of saturated sodium bicarbonate. The organic layer was separated, washed with 500 ml. of fresh bicarbonate, dried over anhydrous magnesium sulfate, filtered, and evaporated to an oil. Trituration with two 100 ml. portions of hexane gave the title product (2.3 g., m.p. 107-110°C.; m/e -265/263).

PREPARATION 4Ethyl 2-(6-Chloro-8-quinolyl)-2-hydroxyacetate

Sodium borohydride (2.5 g., 0.066 mole) was dissolved in 300 ml. of ethanol at 10°C. and added in one portion to a 10°C. solution of product of the preceding Preparation (2.0 g., 0.0076 mole) in 200 ml. of ethanol. After a few minutes, the reaction mixture was diluted with 750 ml. of ethyl acetate and 750 ml. of water. The aqueous layer was extracted with 250 ml. of fresh ethyl acetate. The organic layers were combined, washed with three 250 ml. portions of brine, dried over anhydrous magnesium sulfate, filtered and evaporated to yield title product, initially an oil which crystallized on standing (1.87 g.; m.p. 121-124°C., m/e 267/265).

PREPARATION 5Ethyl 2-(6-Fluoro-8-quinolyl)-2-oxoacetate

By the procedure of Preparation 3, 8-bromo-6-fluoroquinoline [J. Het. Chem., 6, pp. 243-245 (1969); 4.5 g., 0.02 mole] was converted to hexane triturated title product (1.6 g.; m.p. 114-117°C.).

PREPARATION 6Ethyl 2-(6-Fluoro-8-quinolyl)-2-hydroxyacetate

By the procedure of Preparation 4, product of the preceding Preparation (1.5 g., 6.1 mmoles) was converted to title product. The product, initially obtained as a turbid oil, was taken back up in ethyl acetate, washed with brine, dried, filtered and evaporated to an oil which rapidly crystallized (1.23 g., m.p. 84-87°C.).

PREPARATION 76-Hydroxyquinoline-5-carbaldehyde

Sodium hydroxide (25 g.) was dissolved in 35 ml. of water with cooling, 6-hydroxyquinoline (5 g.) in 15 ml. of chloroform was added and the reaction mixture heated to reflux (about 90°C.) for 12 hours, during which two further 15 ml. portions of chloroform were added - one after 2 hours and the other after 6 hours. The reaction mixture was cooled and crude product recovered by filtration. The crude was dissolved in 125 ml. of hot water treated with activated carbon, filtered hot, cooled and acidified with acetic acid and filtered to yield title product [2.5 g.; m.p. 136-137°C.; m/e 173; pnmr/ CDCl₃ shows aldehyde proton at 10.5 ppm and aromatic protons at 7.2-9.4 ppm.].

PREPARATION 86-Methoxyquinoline-5-carbaldehyde

Product of the preceding Preparation (1.7 g., 9.8 mmoles) in 85 ml. of acetone was combined with potassium carbonate (1.21 g., 8.8 mmoles). Dimethyl sulfate (0.83 ml., 8.8 mmoles) was added and the mixture stirred at room temperature for 16 hours. Additional potassium carbonate (0.34 g., 2.5 mmole) and dimethyl sulfate (0.23 ml., 2.5 mmole) were added and the mixture stirred 4 more hours at room temperature and then 3 hours at 60°C. The reaction mixture was cooled to room temperature, salts removed by filtration, and the filtrate evaporated to dryness. The residue was taken up in ethyl acetate, washed sequentially with two portions of 1N ammonium hydroxide, one of water and one of brine, dried over anhydrous magnesium sulfate, filtered and evaporated to yield title product [0.78 g.; Rf 0.35 (2:1 ethyl acetate:chloroform); pnmr/ CDCl_3 /delta (ppm): 4.2 (s, 3H), 7.4-9.1 (m, 5H), 10.3 (s, 1H)].

PREPARATION 97-Hydroxyquinoline-8-carbaldehyde

By the procedure of the Preparation 7, 7-hydroxyquinoline (5 g.) was converted to title product (3.3 g., m.p. 127-130°C.; m/e 173; pnmr/ CDCl_3 shows aldehyde proton at 10.8 ppm, aromatic protons at 7.0-8.9 ppm).

PREPARATION 107-Methoxyquinoline-8-carbaldehyde

By the procedure of Preparation 8, the product of the preceding Preparation (3.3 g., 19 mmoles) was converted to title product [2.1 g., pnmr/ CDCl_3 /delta (ppm): 4.1 (s, 3H), 7.5-9.0 (m, 5H), 11.2 (s, 1H)].

PREPARATION 11

6-Chlorochroman

Mossy zinc (75 g.), 7.5 g. of mercuric chloride, 125 ml. of water and 4 ml. of conc. hydrochloric acid were combined, shaken for 5 minutes, allowed to settle, and liquids decanted from the resulting amalgamated zinc. A mixture of 100 ml. of water and 126 ml. of conc. hydrochloric acid and then 6-chloro-4-chromanone (15 g.) were added to the metal, and the mixture refluxed for 1.5 hours, cooled to room temperature, decanted from the zinc and the decant extracted with three portions of ether. The combined extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to an oil (14 g.). The oil was chromatographed on 400 g. of silica gel using 9:1 hexane: ether as eluant tlc monitoring and 15 ml. fractions. Clean product fractions were combined and evaporated to yield title product as an oil [8.72 g.; $\text{pnmr}/\text{CDCl}_3/\delta$ (ppm) 2.0 (m, 2H), 3.7 (t, 2H), 4.1 (t, 2H), 6.9 (m, 3H); m/e 170/168; Rf 0.88 (2:1 hexane: ether)].

PREPARATION 12

6-Chlorochroman-8-carbaldehyde

Product of the preceding Preparation (8.6 g., 0.051 mole) in 75 ml. of methylene chloride was cooled in an ice-water bath. Titanium tetrachloride (19.34 g., 11.2 ml., 0.102 mole) was added, followed by the dropwise addition of 1,1-dichloromethyl methyl ether (6.2 g., 0.054 mole). The reaction mixture was stirred at 0° for 30 minutes, then slowly poured into 400 ml. of saturated sodium bicarbonate. The aqueous phase was extracted with three fresh portions of methylene chloride. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated to yield title product [7.9 g.; m.p. 83-86°C.; $\text{pnmr}/\text{CDCl}_3/\delta$ (ppm) 2.0 (m, 2H), 2.8 (t, 2H), 4.2 (t, 2H), 7.1-7.5 (m, 2H), 10.2 (s, 1H), m/e 198/196].

PREPARATION 136-Fluorochroman

By the procedures of Preparation 11, 6-fluoro-4-chromanone (15 g.) was converted to chromatographed 6-fluorochroman [5.7 g.; oil; $\text{pnmr}/\text{CDCl}_3/\delta$ (ppm) 2.0 (m, 2H), 3.8 (t, 2H), 4.1 (t, 2H), 6.8 (m, 3H); R_f 0.68 (2:1 hexane:ether); m/e 152].

PREPARATION 146-Fluorochroman-8-carbaldehyde

By the procedures of Preparation 12, the product of the preceding Preparation (5.5 g., 0.036 mole) was converted to title product initially isolated as a viscous oil which was crystallized from hexane (3.4 g.; m.p. 54-57°C.; m/e 180).

PREPARATION 153-Methyl-5-isoxazolecarboxamide

3-Methyl-5-isoxazolecarboxylic acid (20 g.) was refluxed for 10 hours in 350 ml. of thionyl chloride, then stirred at room temperature for 16 hours, clarified by filtration and evaporated to an oil. The oil was multiply triturated with hot hexane, and the combined hexane triturates evaporated to yield acid chloride (16.2 to 21 g.) as a solid.

With stirring, acid chloride prepared in the manner (35 g.) was added portionwise to 300 ml. of conc. ammonium hydroxide at room temperature. After granulating for 1 hour, title product was recovered by filtration (24.2 g., m.p. 180-182°C.).

PREPARATION 163-Methyl-5-isoxazolecarbonitrile

Product of the preceding Preparation (5 g.) was mixed thoroughly with phosphorous pentoxide (10 g.) and placed in an oil bath preheated to 140°. The bath temperature was increased to 200°C. and title product recovered by distillation in vacuo [2.9 g., ir(film) nitrile band at 2220 cm^{-1} , no amide peak in the 1700 cm^{-1} region].

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PREPARATION 173-Methyl-5-isoxazolecarbaldehyde

Product of the preceding Preparation (1.08 g., 0.01 mole) was dissolved in 25 ml. of ether and cooled to -40°C. Diisobutylaluminum hydride (12 ml. of 1M in hexane, 0.012 mole) was added at -40°C. over a 15 minute period. The mixture was stirred at -30° to -35°C. for 10 minutes. Keeping the temperature at -20°C., 60 ml. of ethyl acetate was added. Keeping the temperature at -25°C., methanol (15 ml.) was added dropwise, and keeping the temperature below -20°C., 3 ml. of 6N hydrochloric acid was added. The reaction mixture was warmed to 5°C. and the organic phase washed with 25 ml. of water and evaporated to an oil. The oil was chromatographed on 50 ml. of silica gel using 1:1 ether:hexane as eluant. Product fractions were combined and evaporated to yield title product (0.42 g.; m.p. 39-41°C.). A small sample further purified by sublimation had m.p. 43-45°C.

PREPARATION 18

5-Chlorobenzo[b]furan-2-carboxylic Acid

5-Chlorosalicylaldehyde (31.3 g., 0.2 mole) was dissolved in 200 ml. of 2-butanone. Potassium carbonate (82.9 g., 0.6 mole) and then diethyl 2-bromomalonate (95.6 g., 0.4 mole) were added and the mixture heated to reflux for five hours, then cooled, filtered from salts, and concentrated to an oil. The oil was partitioned between 500 ml. of 10% sulfuric acid and 500 ml. of ether. The aqueous layer was extracted with two 250 ml. portions of fresh ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to a second oil. The second oil was dissolved in 400 ml. of 10% ethanolic potassium hydroxide, heated at reflux for 1 hour and concentrated to solids. The solids were dissolved in 1500 ml. of water, filtered from trace insoluble matter, acidified with 6N hydrochloric acid and precipitated solids recovered by filtration. Purified title product was obtained by repulping the solids in 1 liter of water (19 g., m.p. 259-262°C., m/e 198/196).

By the same procedure, 5-fluorosalicylaldehyde and 6-chlorosalicylaldehyde are converted, respectively, to 5-fluorobenzo[b]furan-2-carboxylic acid and 6-chlorobenzo[b]furan-2-carboxylic acid.

PREPARATION 195-Chlorobenzo[b]furan

Title compound of the preceding Preparation (7.8 g.) was combined with copper powder (700 mg.) and quinoline (50 ml.) and the mixture heated to reflux for 50 minutes, then cooled to room temperature and diluted with 500 ml. of ether. Insolubles were removed by filtration and the filtrate washed in sequence with five 200 ml. portions of 2N hydrochloric acid and one of brine, dried over anhydrous magnesium sulfate and concentrated to an oil (6.2 g.). The oil was chromatographed through 200 g. of silica gel using ether as eluant and 300 ml. fractions. Fractions 1 and 2 were combined and evaporated to yield title product as an oil (6.1 g.).

By the same procedure the other benzofurancarboxylic acids of the preceding Preparation are converted to 5-fluorobenzo[b]furan and 6-chlorobenzo[b]furan.

PREPARATION 205-Chloro-2,3-dihydrobenzo[b]furan

Pd/C (5%, 12.2 g.) in 400 ml. of acetic acid was prehydrogenated at atmospheric pressure and 25°C.

5 Title compound of the preceding Preparation (6.1 g.) in 100 ml. of acetic acid was added and hydrogenation continued until slightly more than 1 equivalent of hydrogen had been consumed. Catalyst was recovered by filtration over diatomaceous earth. The filtrate was
10 neutralized with saturated potassium carbonate and extracted with four 200 ml. portions of ether. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated to an oil. The oil was chromatographed on 400 g. silica
15 gel using hexane-3% ether as eluant, 15 ml. fractions and tlc monitoring. Pure product fractions 70-90 were combined and evaporated to yield title product [2.15 g.; oil; Rf 0.32 (hexane); m/e 156/154].

By the same procedure, the other benzofurans of
20 the preceding Preparation are converted to 5-fluoro-2,3-dihydrobenzo[b]furan and 6-chloro-2,3-dihydrobenzo[b]furan.

PREPARATION 215-Chloro-2,3-dihydrobenzo[b]furan-7-carbaldehyde

By the procedure of Preparation 12, title compound of the preceding Preparation (2.1 g.) was converted to
25 crude product contaminated with an isomeric aldehyde. Purified title product was obtained by digesting the crude product in 50 ml. of boiling hexane, filtering and cooling the filtrate [0.93 g.; m.p. 79-81°C.; Rf 0.55 (chloroform); m/e 184/182].

30 By the same method the 5-fluoro compound of the preceding Preparation is converted to 5-fluoro-2,3-dihydrobenzo[b]furan-7-carbaldehyde.

By the method of Preparation 3, the 6-chloro compound is converted to ethyl 2-(6-chloro-2,3-dihydro-7-benzo[b]furanyl)-2-oxoacetate; then by the method of
35 Preparation 4 to ethyl 2-(6-chloro-2,3-dihydro-7-benzo[b]furanyl)-2-hydroxyacetate.

PREPARATION 227-Chloroquinoline-8-carbaldehyde

5 7-Chloro-8-methylquinoline (1 g.) [Bradford et
al., J. Chem. Soc., p. 437 (1947)] is dissolved in
20 ml. of benzene and brominated with one equivalent of
N-bromosuccinimide in the presence of catalytic amounts
of peroxide. The product, 7-chloro-8-(bromomethyl)-
quinoline is isolated by evaporation.

10 The bromo compound is solvolyzed to 7-chloro-8-
(hydroxymethyl)quinoline by warming with excess alco-
holic potassium hydroxide. To isolate the product, the
reaction mixture is neutralized with hydrochloric acid,
salts separated by filtration and the filtrate evapo-
rated to dryness.

15 The alcohol (1 g.) is dissolved in 10 ml. of
methylene chloride and added dropwise to a slurry of
1.5 equivalents of pyridinium chlorochromate in 20 ml.
of methylene chloride. The exothermic reaction is
controlled by rate of addition, use of a reflux con-
20 denser and occasional cooling in a cooling bath. The
reaction mixture is diluted with ether, and the super-
natant separated by decantation and filtration. The
product is purified by filtration through a short
magnesium silicate column with ether as eluant and
25 isolated by removal of the solvent in vacuo.

PREPARATION 233-Furaldehyde

3-Furylmethanol (19.6 g., 0.2 mole) in 50 ml. of methylene chloride was added dropwise to a slurry of pyridinium chlorochromate (64.5 g., 0.3 mole) in 450 ml. of methylene chloride. The exothermic reaction, which led to vigorous reflux, was controlled by occasional cooling with an ice-bath. By the end of 60 minutes, gummy solids had precipitated. The reaction mixture was diluted with 600 ml. of ether and the supernatant separated by a combination of decantation and filtration. The filtrate was passed through "Florisil" (synthetic magnesium silicate) contained in a short column, with ether as eluant. Collected fractions were combined and evaporated to an oil. Distillation of the oil provided 3-furaldehyde (7.6 g.; b.p. 68-72°C./40-45 mm.). ("Florisil" is a registered Trade Mark).

Alternatively, this aldehyde is prepared by Rosenmund reduction of 3-furoic acid chloride [Hayes, J. Am. Chem. Soc. 71, 2581 (1949)].

PREPARATION 242-(2-Furyl)-1,3-dioxolane

2-Furaldehyde (42 ml., 0.5 mole), ethyleneglycol (50 ml., 0.9 moles) and p-toluenesulfonic acid (about 200 mg.) were combined in 150 ml. of toluene and the mixture refluxed for 6 hours while collecting by-product water in a Dean-Stark trap. The mixture was cooled, diluted with 500 ml. of ether, and clarified by filtration. The filtrate was washed with 200 ml. of saturated sodium bicarbonate and the organic phase again clarified by filtration. This second filtrate was washed with 200 ml. of water, and the organic layer concentrated to dryness, affording 2-(2-furyl)-1,3-dioxolane as an oil (45 g.).

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PREPARATION 252-(5-Chloro-2-furyl)-1,3-dioxolane

2-(2-Furyl)-1,3-dioxolane (14 g., 0.1 mole) was dissolved in 100 ml. of tetrahydrofuran and the solution cooled to -25° to -20°C . Maintaining this temperature range, butyl lithium in hexane (45 ml. of 2.2M, 0.1 mole) was added over a period of 10 minutes. The mixture was allowed to warm to 0°C . over 25 minutes and rechilled to -30°C . While maintaining a temperature range of -30° to -25°C ., hexachloroethane (23.7 g., 0.1 mole) in 50 ml. of tetrahydrofuran was added over 5 minutes. The reaction mixture was warmed to room temperature, stirred for 1.5 hours, recooled to 5°C ., and diluted slowly with 500 ml. of water. Product was extracted into ether (2 x 500 ml.) and recovered as an oil (15.8 g.) by evaporation to dryness. The oil was chromatographed on a 200 ml. volume of silica gel, using 8:1 hexane:ethyl acetate as eluant and monitoring by silica gel tlc with the same eluant. The early, product containing fractions were combined and evaporated to yield purified 2-(5-chloro-2-furyl)-1,3-dioxolane as an oil [5 g.; R_f 0.6 (8:1 hexane:ethyl acetate)].

PREPARATION 265-Chloro-2-furaldehyde

2-(5-Chloro-2-furyl)-1,3-dioxolane (4.8 g.) was dissolved in 20 ml. of ether. 6N Hydrochloric acid (10 ml.) was added and the two-phase mixture stirred for 1 hour at room temperature. The ether phase was separated, washed with water and evaporated to yield 5-chloro-2-furaldehyde as an oil (2.8 g.).

PREPARATION 275-Bromo-2-furylcarboxamide

5-Bromo-2-furoic acid (20 g.) was refluxed for 3 hours with 60 ml. of thionyl chloride, and the corresponding acid chloride isolated as an oil by concentration. The acid chloride was added dropwise to 150 ml. of stirring, concentrated ammonium hydroxide. Filtration afforded 5-bromo-2-furylcarboxamide (17.0 g., m.p. 140-143°C.).

PREPARATION 285-Bromo-2-furylcarbonitrile

5-Bromo-2-furylcarboxamide (10 g.) was combined with 50 ml. of phosphorus oxychloride and refluxed for 24 hours. The mixture was poured onto ice, the product extracted into ether, which on evaporation gave 5-bromo-2-furylcarbonitrile as an oil (6.4 g.).

PREPARATION 295-Bromo-2-furaldehyde

5-Bromo-2-furylcarbonitrile (2.3 g., 13 mmoles) was dissolved in 50 ml. of ether and cooled, under nitrogen, to -10°C. Diisobutylaluminum hydride (1.9 g., 13 mmoles) as a 25% solution in toluene was added dropwise, maintaining the temperature near -10°C. The reaction was allowed to warm to room temperature and allowed to stir about 6 hours. The reaction mixture was cooled to 0° to 5°C., diluted with 1 ml. of methanol, acidified with 3N hydrochloric acid, washed with water, and evaporated to yield 5-bromo-2-furaldehyde (1.2 g., m.p. 74-76°C.).

PREPARATION 30

3-Bromo-2-furaldehyde

Phosphorus oxychloride (6.5 g., 70 mmoles) was added to dimethylformamide (5.4 g., 70 mmoles) at 0° to 10°C. The resulting slurry was diluted with 10 ml. of ethylene dichloride. Maintaining the mixture near 10°C., 3-bromofuran (9.2 g., 63 mmoles) was added. The reaction mixture was then heated to 58-60°C. for 1 hour and then recooled to 10°C. Sodium acetate trihydrate (15 g.) dissolved in 25 ml. of water was added slowly, with good stirring, keeping the temperature 10° to 30°C. The mixture was reheated to 68-72°C. for 20 minutes, cooled to room temperature, and diluted with 20 ml. of water. Product was extracted into 75 ml. of ether, and the ether back-washed with water and concentrated to yield 3-bromo-2-furaldehyde as an oil [0.9 g., R_f 0.65 (3:1 hexane:ethyl acetate)].

PREPARATION 31

3-Iodofuran

3-Bromofuran (14.7 g., 0.1 mole) in 100 ml. of ether was cooled to -70°C. Butyl lithium (42 ml. of 2.4M, 0.1 mole) in hexane was added dropwise over 0.5 hour, maintaining the temperature from -70° to -65°C. Iodine (25 g., 0.1 mole) in 200 ml. of ether was then added over 1 hour maintaining the same temperature range. The reaction mixture was warmed to room temperature and then back to 2°C. Water (100 ml.) was added dropwise. The ether layer was separated, washed with aqueous thiosulfate and then water, dried over anhydrous sodium sulfate, evaporated to an oil and distilled to yield 3-iodofuran (15.7 g., b.p. 48°/28 mm.).

PREPARATION 323-Methoxyfuran

Sodium metal (5.6 g., 0.24 mole) was dissolved in 150 ml. of dry methanol. 3-Iodofuran (15.7 g., 0.08 mole) and cuprous oxide (8 g., 0.1 mole) were added and the mixture was refluxed with vigorous stirring for 42 hours. The reaction mixture was cooled to room temperature, diluted with 200 ml. of water, and product extracted into 100 ml. of ether. The ether extract was back-washed with 15 ml. of water, dried over anhydrous sodium sulfate and evaporated to yield crude 3-methoxyfuran (approximately 3-4 g. of approximately 50% purity) suitable for further processing.

PREPARATION 335-Phenyl-2-thenaldehyde

1-Phenylthiophene [1.6 g., 0.01 mole, prepared according to J. Am. Chem. Soc. 46, 2339 (1924)] was dissolved in 20 ml. of tetrahydrofuran and cooled to -40°C. Butyl lithium in hexane (4.5 ml. of 2.2M) was added over 3 minutes, maintaining the temperature -40° to -30°C. The mixture was warmed to 0°C. and then cooled to -40°C. Dimethylformamide (1.2 ml., 15 mmole) was added, maintaining the temperature -40° to -30°C. The mixture was warmed to room temperature and held for 0.5 hour, recooled to 0°C., quenched with 6 ml. of 6N hydrochloric acid, diluted with 10 ml. of water, and extracted with 20 ml. of ether. Evaporation of the ether extract to dryness gave crude product (1.9 g.). Recrystallization from about 35 ml. of hexane gave purified 5-phenyl-2-thenaldehyde (0.9 g., m.p. 90-92°C.).

(B)

PREPARATION 344-Bromo-3-thenaldehyde

3,4-Dibromothiophene [15 g., 0.062 mole, J. Org. Chem. 36, 2690 (1971)] in 20 ml. of ether was cooled to -70°C. and butyl lithium in hexane (34.8 ml. of 2.1M, 0.073 mole) added dropwise over 5 minutes. After stirring for 5 minutes at -70°C., the solution was transferred, via nylon tubing under nitrogen pressure, to a solution of dimethylformamide (6.8 g., 0.093 mole) in 35 ml. of ether. The resulting mixture was heated to reflux for 2 hours, cooled to room temperature, washed in sequence with two portions of 1N hydrochloric acid, one of saturated sodium bicarbonate and one of brine, dried over anhydrous magnesium sulfate, filtered and concentrated to an oil. The oil was twice distilled to yield 4-bromo-3-thenaldehyde (5.7 g., b.p. 81-84°C./0.8 mm., m/e 192/190).

PREPARATION 352-Phenylfuran

Aniline (46.5 g., 0.5 mole) was combined with 500 ml. of water and 100 ml. of concentrated hydrochloric acid and cooled to -5°C . Sodium nitrite (36.2 g., 0.525 mole) in 100 ml. of water was added dropwise over 45 minutes, keeping the temperature -3° to -5°C . After addition was complete, the mixture was stirred for 30 minutes at -5°C ., and zinc chloride (68 g.) was added. Maximal precipitation of the diazonium salt was obtained by the addition of 100 g. of sodium chloride. The mixture was stirred for 5 minutes, with the cooling bath removed and cautiously filtered, without wash, and air dried for 2 hours. (Previous vacuum drying of this product led to explosive decomposition). The intermediate diazonium salt was suspended in 750 ml. of furan at 0°C . With vigorous stirring, powdered sodium hydroxide (5 g.) was added, followed by anhydrous sodium acetate (10 g.). The reaction mixture was stirred for 5 hours at 0°C . and then for 16 hours at room temperature. Solids were removed by filtration and the filtrate evaporated to crude product (25 ml. of oil). Distillation afforded 1-phenylfuran (9.2-9.6 g., b.p. $87-95^{\circ}/15\text{ mm.}$, b.p. $50^{\circ}/1\text{ mm.}$).

PREPARATION 362-Phenyl-2-(2-thienyl)-1,3-dioxolane

2-Benzoylthiophene (19 g., 0.1 mole), ethylene glycol (11 ml., 0.2 mole), toluene (150 ml.) and p-toluenesulfonic acid (about 0.2 g.) were combined and refluxed for 6 hours. By-product water was collected in a Dean-Stark trap. Tlc (1:8 ethyl acetate:hexane) indicated reaction to be about 40% complete. More ethylene glycol (30 ml.) was added and reflux continued for 35 hours. Reaction was still incomplete. The reaction mixture was diluted with 200 ml. of ether, washed twice with 150 ml. portions of water and concentrated to dryness. The residue was chromatographed on about 500 ml. of silica gel, with 1:8 ethyl acetate:hexane as eluant, monitored by tlc. Faster moving, product containing fractions were combined and evaporated to yield 2-phenyl-2-(2-thienyl)-1,3-dioxolane [8 g., oil, R_f 0.6 (1:8 ethyl acetate:hexane)].

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PREPARATION 37

Methyl 4-Methoxy-3-thenoate

Methyl 4-acetoxy-3-thenoate (U.S. Patent 3,144,235; 10 g.) was dissolved in 20 ml. of methanol and added
5 to 100 ml. of methanol containing 0.31 ml. of concentrated sulfuric acid. The mixture was refluxed for 4 days, then neutralized with 0.6 g. of sodium acetate and solvent removed by evaporation. The residue was
10 taken up in 200 ml. of ether. The ether solution was washed sequentially with two 50 ml. portions of water, two 50 ml. portions of 1N sodium hydroxide and two 50 ml. portions of brine, dried over anhydrous magnesium sulfate, filtered and evaporated to an oil which crystallized on standing (4.35 g.; m.p. 64-66°C).
15 When this reaction was worked up after only 1 day only a low yield of the desired product (2.2 g) was isolated. The two 1N sodium hydroxide extracts were combined and acidified, precipitating methyl 4-hydroxy-3-thenoate (5.13 g.). When this alcohol was
20 dissolved in 100 ml. of methanol containing 0.3 ml. of concentrated sulfuric acid and refluxed for 3 days, the above work-up afforded title product (2.10 g., m.p. 64-66°C.).

PREPARATION 381-(4-Methoxy-3-thienyl)methanol

Methyl 4-methoxy-3-thenoate (U.S. Patent 4,144,235; 3.9 g., 23 mmoles) was dissolved in 50 ml. of toluene and cooled in an acetone-dry ice bath. Diisobutyl aluminum hydride (46 ml. of 1M in hexane, 46 mmoles) was added dropwise over 30 minutes. The mixture was stirred for an additional 2 hours at the bath temperature and then allowed to warm to room temperature. Keeping the temperature below 30°C., methanol (14.7 g., 18.6 ml., 0.46 mole) was slowly added. The mixture was then stirred for 16 hours at room temperature, by which time a granular precipitate had formed. The mixture was filtered over diatomaceous earth with methanol wash. The combined filtrate and washes were concentrated to yield the title product as an oil (2.8 g., m/e 144).

PREPARATION 394-Methoxy-3-thenaldehyde

Pyridinium chlorochromate (6.4 g., 29.7 mmoles) was dissolved in 100 ml. of methylene chloride and added in one portion to a solution of the product of the preceding Example (2.8 g., 19.8 mmoles) also in 100 ml. of methylene chloride. The reaction mixture was stirred at room temperature for three hours, diluted with 200 ml. of ether and decanted from the black precipitate. The precipitate was washed with two 100 ml. portions of ether. The combined decant and washes were filtered, washed in sequence with two portions of 1N hydrochloric acid, one portion of water, two portions of 1N sodium hydroxide and one portion of brine, dried over anhydrous magnesium sulfate, filtered and concentrated to yield title product as an oil [2.6 g.; m/e 142; ir (CH_2Cl_2) 1688, 1544 cm^{-1}].

PREPARATION 40Ethyl 4-Ethoxy-3-thenoate

Following the approximate procedure of U.S. 4,144,235, methyl 4-acetoxy-3-thenoate (20 g.) was dissolved in 240 ml. of ethanol and 0.62 ml. of concentrated sulfuric acid was added. The reaction mixture was gently refluxed for 79 hours, then neutralized with sodium acetate (1.2 g.) and evaporated to an oil. The latter was partitioned between 400 ml. of ether and 50 ml. of water. The organic layer was separated and washed in sequence with 75 ml. of water, three 50 ml. portions of 1N sodium hydroxide and two 75 ml. portions of brine, dried over anhydrous magnesium sulfate, filtered and evaporated to yield title product as an oil [14.9 g., pmr indicates entirely ethyl ester, no methyl ester].

PREPARATION 411-(4-Ethoxy-3-thienyl)methanol

By the procedure of Preparation 38, the product of the preceding Preparation (14 g.) was converted to title product as an oil (9.15 g.).

PREPARATION 424-Ethoxy-3-thenaldehyde

By the procedure of Preparation 39, the product of the preceding Preparation (9.15 g.) was converted to the title product, initially isolated as an oil which quickly crystallized on cooling [8.18 g.; m.p. 42-45°C.; m/e 156; ir (KBr) 3090, 2977, 1688 cm^{-1}].

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PREPARATION 43n-Propyl 4-(n-Propoxy)-3-thenoate

By the procedure of Preparation 40, using a reaction reflux time of 10 days, methyl 4-acetoxy-3-thenoate (6 g.) in 750 ml. of 1-propanol containing 0.19 ml. of concentrated sulfuric acid was converted to title product as an oil (5.4 g.; m/e 228).

PREPARATION 441-[4-(n-Propoxy)-3-thienyl]methanol

By the procedure of Preparation 38, the product of the preceding Preparation (5.4 g.) was reduced to title compound, isolated as an oil (3.44 g.; m/e 172).

PREPARATION 454-(n-Propoxy)-3-thenaldehyde

By the procedure of Preparation 39, the product of the preceding Preparation (3.34 g.) was converted to title compound [3.19 g.; m/e 170; ir (CH_2Cl_2) 1689, 1539 cm^{-1}].

PREPARATION 46Ethyl 4-Methoxy-2-methyl-3-thenoate

Ethyl 4-hydroxy-2-methyl-3-thenoate [Chem. Ber. 48, p. 593 (1915); 7.8 g.] was combined with 600 ml. of methanol and 0.25 ml. concentrated sulfuric acid and refluxed for 21 hours. The reaction mixture was evaporated to an oil, taken up in 500 ml. of ether, washed with two 50 ml. portions of 1N sodium hydroxide and then one of brine, dried over anhydrous magnesium sulfate, and evaporated to yield title product as an oil (7.8 g.; m/e 200; pnmr/ CDCl_3 includes singlet OCH_3 protons at 3.9 ppm). The product is contaminated with a minor portion of the corresponding methyl ester.

PREPARATION 47(4-Methoxy-2-methyl-3-thienyl)methanol

The product of the preceding Preparation (7.8 g., 0.039 mole) was dissolved in 100 ml. of hexane and 75 ml. of toluene and cooled to -78°C . Diisobutyl aluminum hydride (78 ml. of 1M in hexane, 0.078 mole) was added dropwise over 40 minutes. The mixture was stirred for 2 hours at -78°C ., warmed to room temperature and stirred for an additional 16 hours. Methanol (25.0 g., 31.6 ml., 0.78 mole) was added dropwise to the reaction mixture, keeping the temperature below 30°C . After stirring 1.5 hours at room temperature, the reaction mixture was clarified by filtration over diatomaceous earth, with thorough methanol wash and repulp of the cake and finally methylene chloride wash. The combined filtrate and washes were dried over anhydrous magnesium sulfate, filtered and evaporated to yield title product as an oil (5.56 g.; m/e 158; ir (CH_2Cl_2) $3598, 1582, 1708\text{ cm}^{-1}$).

PREPARATION 484-Methoxy-2-methyl-3-thenaldehyde

By the procedure of Preparation 39, the product of the preceding Preparation (5.4 g., 0.034 mole) was converted to title compound isolated as an oil [5.23 g.; R_f 0.36 (chloroform)].



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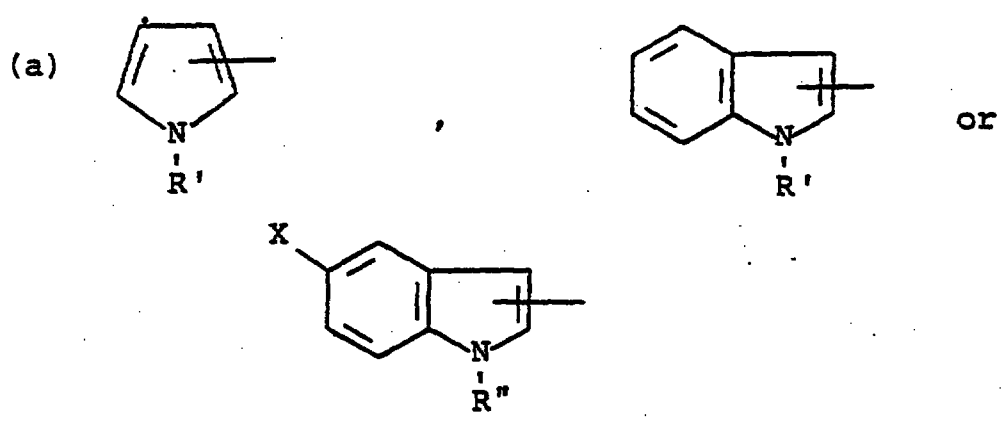
CLAIMS

1. A racemic or optically active compound of the formula

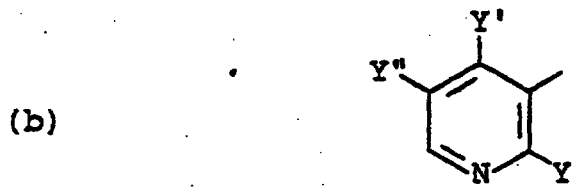


wherein

R is hydrogen, (C₁-C₄)alkanoyl, benzoyl, (C₂-C₄)-carbalkoxy, (C₁-C₃)alkylcarbamoyl, (C₅-C₇)cycloalkyl-carbamoyl or di(C₁-C₃)alkylcarbamoyl; and
R¹ is



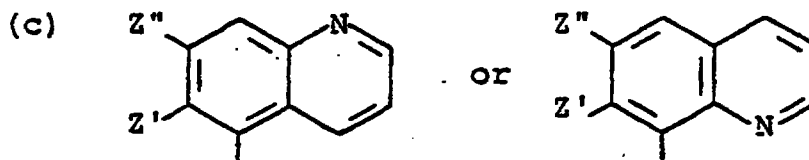
wherein R' is (C₁-C₄)alkyl or phenyl, R'' is hydrogen, (C₁-C₄)alkyl or phenyl and X is halo;



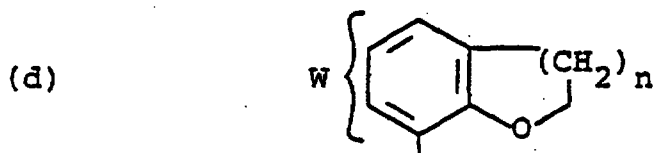


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wherein Y is hydrogen or (C_1-C_3) alkoxy, Y' is hydrogen or (C_1-C_3) alkyl and Y'' is hydrogen or halo;



wherein Z' is hydrogen, halo or (C_1-C_3) alkoxy and Z'' is hydrogen or halo;



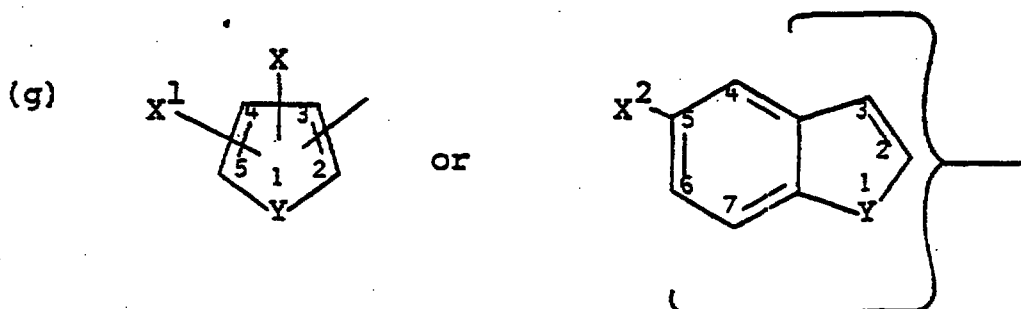
wherein W is hydrogen or halo, and n is 1 or 2;

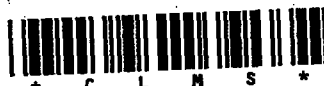


wherein Q is sulfur or oxygen and V is hydrogen or (C_1-C_3) alkyl;



wherein Q is sulfur or oxygen; and V is hydrogen or (C_1-C_3) alkyl; or





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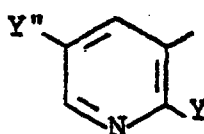
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wherein Y is sulfur or oxygen; X is hydrogen, halo, methyl, phenyl, benzoyl or (C₁-C₃)alkoxy; X¹ is hydrogen or methyl; and X² is hydrogen or halo;

or a pharmaceutically-acceptable cationic salt thereof when R is hydrogen;

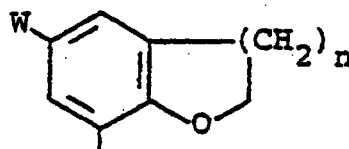
or a pharmaceutically-acceptable acid addition salt thereof when R¹ contains a basic nitrogen functionality.

2. A compound of claim 1 wherein R¹ is



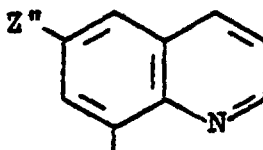
Y is (C₁-C₂)alkoxy and Y'' is hydrogen, chloro or fluoro.

3. A compound of claim 1 wherein R¹ is



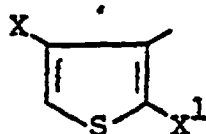
W is chloro or fluoro, and n is 1 or 2.

4. A compound of claim 1 wherein R¹ is

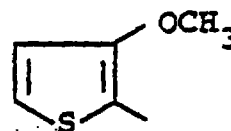


and Z'' is chloro or fluoro.

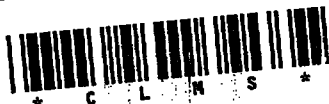
5. A compound of claim 1 wherein R¹ is



or



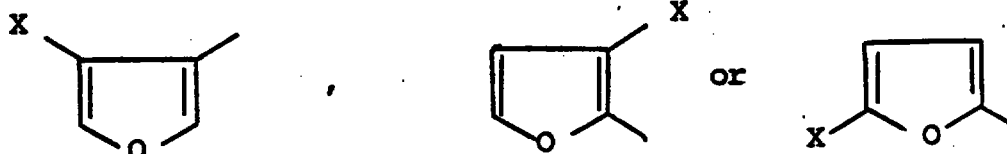
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X is (C₁-C₂)alkoxy and X¹ is hydrogen or methyl.

6. A compound of claim 1 wherein R¹ is



and X is hydrogen or halo.

7. A pharmaceutical composition comprising a compound of the formula (I) or a salt thereof as claimed in any one of claims 1 to 6 together with a pharmaceutically acceptable diluent or carrier.

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