PATENT SPECIFICATION

(11) 1 262 292

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NO DRAWINGS

(21) Application No. 16909/68 (22) Filed 9 April 1968

(23) Complete Specification filed 2 April 1969

(45) Complete Specification published 2 Feb. 1972

(51) International Classification C 07 d 91/24, 91/32; A 61 k 27/00

(52) Index at acceptance

C2C 170—197—285 171—196—285 1E3K4 1E3K6 1E7B2 1E7C2 1E7D1 1E7E1 1E7H2 1E7N5 1E7P3 1Q11D 1Q11G 1Q4 1Q6C 1Q7A 1Q8A 1Q9D1 1Q9D2 1Q9F2 215 220 226 22Y 246 256 25Y 30Y 315 31Y 332 360 363 366 367 36Y 3A10A4G 3A10A5K 3A7V1A4 3A7V1E2 3A7V1L 3A7V1P 3A7V2A4 3A7V2E1 3A7V2G2 3A7V2L 3A7V3A4 3A7V3E1 3A7V3E2 3A7V3L 3A7V3P 3A7V4A4 3A7V4E1 3A7V4G2 3A7V4L 621 628 658 661 669 672 681 682 790 79Y JA MM

A5B 381 38Y 420 42Y 480 482 48Y 502 50Y 540 543 546 54Y 565 56Y 586 58Y 596 59Y 606 60Y 650 65Y 670 67Y

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(54) NOVEL THIAZOLINE DERIVATIVES, THE PREPARATION THEREOF AND COMPOSITIONS CONTAINING THE SAME

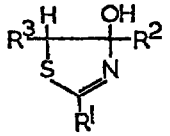
(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, a British Company, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to thiazoline compounds, to a process for the preparation thereof and to pharmaceutical compositions containing such compounds. The invention also relates to the conversion of the thiazoline compounds to thiazoles.

It is known from U.K. Patent Specification No. 1,099,389 that *p*-bromothiobenzamide, on heating with ethyl γ-bromoacetoacetate, gives ethyl 2-(*p*-bromophenyl)thiazol-4-ylacetate. The same specification also discloses that a number of similar thiazoles can be obtained in the same way by using other substituted haloketoesters and other substituted thiobenzamides. Other thiazoles which can be prepared in this way have been described in our U.K. patent specifications 1,145,884; 1,147,626; 1,237,194 and 1,245,087. The products of the inventions disclosed in these applications include thiazoles having two aryl or heteroaryl groups as substituents, as well as thiazoles having a cycloalkyl radical in the 2-position.

We have now found that if the above type of reaction is carried out carefully, it is possible to isolate an intermediate containing a thiazoline structure, and that this intermediate generally exhibits pharmaceutical activity, particularly anti-inflammatory activity, when tested on warm blooded animals. A typical test of this type is based on the inhibition of experimentally induced oedema in rats and is described by Winter *et al* in Proc. Soc. Biol. Med. *III*, 544 (1962) and by Buttle *et al* in Nature, *179*, 629 (1957).

The present invention therefore provides thiazolines of the general formula



(I)

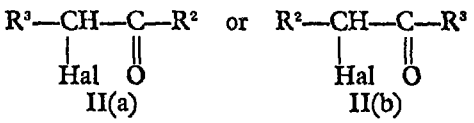
and acid addition salts thereof, in which R^1 is a substituted or unsubstituted aryl radical (which may be a heteroaryl radical) or a cycloalkyl radical, R^2 is a carboxyalkyl radical containing 2 to 6 carbon atoms or an ester, nitrile or amide derivative thereof, R^3 is a hydrogen, lower alkyl or a substituted or unsubstituted aryl radical (which may be a heteroaryl radical) and either the 4- or the 5- position contains the radical R^2, the remaining one of the 4- and 5-positions containing the radical R^3. The terms "lower alkyl" and "lower alkoxy" relate to branched and straight chain residues and have up to 6 carbon atoms.

[*Price 25p*]

SEE ERRATA SLIP ATTACHED

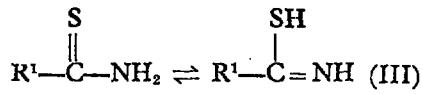
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The compounds of general formula I, in the form of a hydrohalide, may be prepared by reacting a compound of the general formula



II(a) II(b)

with a thioamide of the general formula



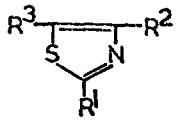
(III)

(where R^1, R^2, and R^3 have the meanings defined above and Hal is a halogen atom) under mild conditions. The temperatures used for the reaction must be below the dehydration temperature of the thiazoline hydrohalide. The optimum temperature will therefore depend on the particular reactants used and temperatures up to 80°C, preferably in most cases below 50°C, can be employed. It is also preferable to carry out the reaction in an inert organic solvent in which the thiazoline hydrohalide formed is insoluble. If R^2 is a carboxyalkyl radical and if the reaction is carried out in isopropanol in the presence of an alkali metal carbonate, the free thiazoline aliphatic acid can be obtained. On the other hand, it is generally more convenient to use a reactant in which R^2 is a lower alkyl ester (i.e. containing 1 to 4 carbon atoms) of an aliphatic acid, e.g. the etnyl ester. Conveniently equimolar amounts of the reactants are used and the reaction mixture is heated to the required temperature, such as 60—70°C, for up to several hours or in some cases is merely kept at room temperature overnight. The thiazolines provided by the invention can be separated in known manner, e.g. by filtration, and the filtrate may be acidified to precipitate additional product.

The thiazoline free bases can be prepared from the hydrohalides by treatment with a base, e.g. an alkali metal carbonate.

R^1 may, for example, be phenyl, halophenyl (e.g. chloro, bromo or fluorophenyl), nitrophenyl, trifluoromethylphenyl, lower alkylphenyl (e.g. methylphenyl), lower alkoxyphenyl (e.g. methoxyphenyl), naphthyl, 2- or 3-furyl, 2- or 3- thienyl, cyclopentyl or cyclohexyl. R^2 can be, for example, an aliphatic acid radical containing 2 to 6 carbon atoms or an ester, nitrile or amide thereof. Examples of preferred radicals R^2 are carboxymethyl, 1-carboxyethyl and 2-carboxyethyl radicals and the methyl and ethyl esters thereof. R^3 preferably is hydrogen, methyl or one of the aryl radicals listed for R^1.

When the 4-hydroxy-thiazolines of the invention are employed as intermediates to prepare the corresponding thiazoles of formula



(IV)

in which R^1, R^2, and R^3 have the meanings defined in connection with formula (I), they can be dehydrated by heating to above the dehydration temperature, if desired in the presence of an acid. The 4-hydroxythiazolines of the invention are readily dehydrated on heating when in the form of an acid addition salt, the free bases being more stable. Dehydration may be effected by heating the compound in the presence or absence of an organic solvent in the presence of a sulphuric acid, e.g. benzensulphonic acid or *p*-toluene-sulphonic acid, using a water separator until water is no longer evolved or more simply by heating in an alkanoic acid such as glacial or aqueous acetic acid. When the reaction is complete the thiazole can be recovered conventionally; for instance the reaction mixture can be evaporated to reduced volume and the product crystallised from a solvent, for instance an alcohol. The thiazoles in general are anti-inflammatory agents when tested on warm blooded animals such as by the above-mentioned test of Winter *et al.* Accordingly, the invention provides a pharmaceutical composition comprising a thiazole prepared by the above mentioned process and a pharmaceutically acceptable carrier.

As the compounds of general formula (I) generally show pharmaceutical activity, for example anti-inflammatory activity, the invention provides a pharmaceutical composition comprising a compound of general formula (I), or an acid addition salt thereof, and a pharmaceutically acceptable carrier.

When the compounds of this invention are employed as anti-inflammatory agents they can be administered to warm-blooded animals, e.g. mice, rats, rabbits, dogs, cats or monkeys, alone or as a pharmaceutical composition in combination with pharmaceutically acceptable carriers. The carrier may be solid, liquid ar cream-like and any suitable carrier known to the art can be used. The composition can be in unit dose form, for example as tablets or capsules or it can be in the form of a solution. The compositions can be administered orally or parenterally by injection and the composition can, for parenteral administration, be in the form of a sterile solution or suspension containing other solutes, for example enough saline or glucose to render the solution isotonic. The particular carrier and proportion of carrier to active compound will be determined by the nature of the compound, the chosen route of administration and standard pharmaceutical practice.

The dosage of the thiazoline will vary with the form of administration and the particular

compound chosen. Furthermore, it will vary with the particular subject under treatment. Generally, treatment is initiated with small dosages which are substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects.

The following Examples illustrate the invention:

EXAMPLE 1.

4 - (p - Bromophenyl) - 4 - hydroxy - 2-phenyl - 2 - thiazoline - 5 - acetic acid

Thiobenzamide (3.43 g.), 3-(*p*-bromobenzoyl)-3-bromo-propionic acid (8.4 g.) and sodium carbonate (1.33 g.) in isopropanol (50 ml.) are stirred at 60—70°C for 1½ hours. The cooled reaction mixture is poured into water and solid sodium carbonate is added carefully until pH 8 is obtained. The basic aqueous solution is extracted with ether, treated with charcoal and filtered. The solid filtrate is collected (6.12 g.). Recrystallisation affords the title compound as colourless micro-needles (3.14 g., 32%) m.p. 135—137°C. Analysis: Found: C, 51.8; H, 3.7; Br, 20.3; N, 3.8; S, 8.3. $C_{17}H_{14}BrNO_3S$ requires C, 52.1; H, 3.6; Br, 20.4; N, 3.6; S, 8.2%.

4 - (*p* - Chlorophenyl) - 4 - hydroxy - 2-phenyl-2-thiazolin-5-acetic acid, 4-(*p*-fluorophenyl) - 4 - hydroxy - 2 - phenyl - 2 - thiazolin-5-acetic acid and 4-(*m*-trifluoromethylphenyl) - 4 - hydroxy - 2 - phenyl - 2 - thiazolin-5-acetic acid can be prepared in a similar manner.

EXAMPLE 2.

4 - (p - Chlorophenyl) - 4 - hydroxy - 2-phenyl - 2 - thiazoline - 5 - acetic acid

A mixture of 3-bromo-3-(*p*-chlorobenzoyl) propionic acid (94.5 g.) anhydrous sodium carbonate (34.3 g.) and isopropanol (200 ml.) are stirred and heated to 60—65°C. The temperature is maintained at this range while thiobenzamide (44.3 g.) is added in portions. After the addition is completed, the mixture is stirred and heated between 60—70°C for an additional one-half hour then left standing at room temperature for eighteen hours. The resulting solid is separated and suspended in water. The mixture is filtered to remove 4-(*p*-chlorophenyl) - 4 - hydroxy - 2 - phenyl - 2 -thiazoline-5-acetic acid (10 g.), m.p. 148—150°C. The aqueous filtrate is acidified with hydrochloric acid to precipitate an additional 48 g. of 4 - (*p* - chlorophenyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid, m.p. 148—150°C. Analysis: Found: C, 58.88; H, 4.02; N, 3.97; Cl, 9.84; S, 9.56. $C_{17}H_{14}ClNSO_3$ requires C, 58.70; H, 4.06; N, 4.03; Cl, 10.20; S, 9.22%.

The above-prepared 4-(*p*-chlorophenyl)-4-hydroxy - 2 - phenyl - 2 - thiazoline - 5-acetic acid (55 g.) is refluxed in toluene, in the presence of *p*-toluene-sulphonic acid, (0.36 g.) in a flask equipped with a water separator until water ceases to evolve. Thereafter, the mixture is evaporated to dryness under vacuum and the residue recrystallised from ethanol to afford 4 - (*p* - chlorophenyl) - 2 - phenyl - 5 - thiazole-acetic acid, m.p. 161—162°C.

Analysis: Found: C, 62.0; H, 3.7; N, 4.2; S, 9.8. $C_{17}H_{12}ClNO_2S$ requires C, 61.9; H, 3.7; N, 4.2; S, 9.7%.

EXAMPLE 3.

4 - Hydroxy - 2 - phenyl - 4 - (*p* - trifluoromethylphenyl) - 2 - thiazoline - 5 - acetic acid

A mixture of 3-bromo-3-(*p*-trifluoromethylphenyl)-propionic acid (11.5 g.), anhydrous sodium carbonate (3.7 g.), isopropanol (100 ml.) and thiobenzamide (4.7 g.) are reacted as in Example 2. This mixture is filtered, the filtrate is evaporated to dryness and an oil residue solidifies on standing. After recrystallisation from aqueous ethanol there is obtained 4 - hydroxy - 2 - phenyl - 4 - (*p* - trifluoromethylphenyl)-2-thiazoline-5-acetic acid, m.p. 160—1°C.

Analysis: Found: C, 56.68; H, 3.57; N, 3.70. $C_{18}H_{14}F_3NSO_3$ requires C, 56.69; H, 3.70; N, 3.68%.

Repeating the procedure of Example 2, the above prepared 4-hydroxy-2-phenyl-4-(*p*-trifluoromethylphenyl)-2-thiazoline-5-acetic acid is converted to the corresponding 2-phenyl-4-(*p*-trifluoromethylphenyl)-5-thiazoleacetic acid, m.p. 168—9°C.

EXAMPLE 4.

4 - (*p* - Bromophenyl) - 4 - hydroxy - 2-phenyl - 2 - thiazoline - 5 - acetic acid

A mixture of 3-bromo-3-(*p*-bromobenzoyl) propionic acid (95 g.), anhydrous sodium carbonate (35 g.), thiobenzamide (45 g.) and ethanol (200 ml.) are stirred at room temperature for one-half hour then left standing at room temperature for twenty hours. The resulting solid is separated and suspended in water. The mixture is filtered to remove 4-(*p*-bromophenyl) - 4 - hydroxy - 2 - phenyl - 2-thiazoline - 5 - acetic acid. Thereafter, the aqueous filtrate is acidified with hydrochloric acid to precipitate additional 4-(*p*-bromophenyl) - 4 - hydroxy - 2 - phenyl - 2 - thiazoline-5-acetic acid.

The above prepared 4-(*p*-bromophenyl)-4-hydroxy - 2 - phenyl - 2 - thiazoline - 5 - acetic acid is refluxed in 50% aqueous acetic acid for 1 hour. On cooling, crystals of 4-(*p*-bromophenyl)-2-phenyl-5-thiazoleacetic acid appear and are separated.

Repeating the above procedure, to react 4-bromo-4-(3'-furoyl)-butyric acid with thiobenzamide, there is obtained 4-(3'-furyl)-4-

hydroxy - 2 - phenyl - 2 - thiazoline - 5 - propionic acid, which is then dehydrated to afford 4 - (3'-furyl) - 2 - phenyl - 5 - thiazolepropionic acid.

EXAMPLE 5.

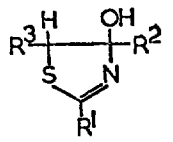
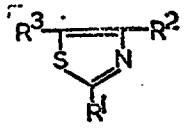
When the procedure of Example 4 is repeated to react the appropriate acid of formula II(b) with thioamides, the following 4-hydroxy-2-thiazoline-5-alkanoic acids are prepared which are then dehydrated to form their corresponding 5-thiazolealkanoic acid.

4-Hydroxy-2-Thiazoline-5-Alkanoic Acids	5-Thiazolealkanoic Acids
4-hydroxy-4-(2-thienyl)-2-(*o*-tolyl)-2-thiazoline-5-acetic acid	4-(2-thienyl)-2-(*o*-tolyl)-5-thiazolacetic acid, m.p. 136—8°C.
2-(*p*-chlorophenyl)-4-hydroxy-4-(*p*-methoxyphenyl)-2-thiazoline-5-acetic acid	2-(*p*-chlorophenyl)-4-(*p*-methoxyphenyl)-5-thiazole-acetic acid, m.p. 199—201°C.
2-(*p*-chlorophenyl)-4-hydroxy-4-phenyl-2-thiazoline-5-acetic acid	2-(*p*-chlorophenyl)-4-phenyl-5-thiazoleacetic acid, m.p. 153—5°C.
2-(*p*-chlorophenyl)-4-hydroxy-4-(2-thienyl)-2-thiazoline-5-acetic acid	2-(*p*-chlorophenyl)-4-(2-thienyl)-5-thiazolacetic acid, m.p. 137—9°C.
4-hydroxy-2,4-bis(*p*-methoxy-phenyl) 2-thiazoline-5-acetic acid	2,4-bis(*p*-methoxyphenyl)-5-thiazoleacetic acid, m.p. 176—8°C.
4-hydroxy-4-(*p*-methoxyphenyl)-2-(o-tolyl) 2-thiazoline-5-acetic acid	4-(*p*-methoxyphenyl)-2-(*o*-tolyl)-5--thiazole-acetic acid, m.p. 140—1°C.
4-hydroxy-4-phenyl-2-(*o*-tolyl)-2-thiazoline-5-acetic acid	4-phenyl-2-(*o*-tolyl)-5-thiazoleacetic acid, m.p. 165—7°C.
4-hydroxy-4-phenyl-2-(*m*-tolyl)-2-thiazoline-5-acetic acid	4-phenyl-2-(*m*-tolyl)-5-thiazoleacetic acid, 123—5°C.
4-hydroxy-2-(*p*-methoxyphenyl)-4-phenyl-2-thiazoline-5-acetic acid	2-(*p*-methoxyphenyl)-4-phenyl-5-thiazole-acetic acid, m.p. 149.5—152°C.
2-(*o*-chlorophenyl)-4-hydroxy-4-phenyl-2-[illegible]iazoline-5-acetic acid	2-(*o*-chlorophenyl)-4-phenyl-5-thiazoleacetic acid, m.p. 168—71°C.
4-hydroxy-4-phenyl-2-(*p*-tolyl)-2-thiazoline-5-acetic acid	4-phenyl-2-(*p*-tolyl)-5-thiazoleacetic acid, acid, m.p. 170—1°C.
4-hydroxy-2-(1-naphthyl)-4-phenyl-2-thiazoline-5-acetic acid	2-(1-naphthyl)-4-phenyl-5-thiazoleacetic acid, m.p. 145—8°C.
4-hydroxy-4-phenyl-2-(*m*-trifluoromethyl-2-thiazoline-5-acetic acid	4-phenyl-2-(*m*-trifluoromethyl-phenyl-5-thiazoleacetic acid, m.p. 143—5°C.
4-hydroxy-2-(*p*-methoxyphenyl)-4-(2-thienyl) 2-thiazoline-5-acetic acid	2-(*p*-methoxyphenyl)-4-(2-thienyl)-5-thiazoleacetic acid, m.p. 149—51°C.

4-Hydroxy-2-Thiazoline-5-Alkanoic Acids	5-Thiazolealkanoic Acids
4-hydroxy-2-(2-naphthyl)-4-phenyl-2-thiazoline-5-acetic acid	2-(2-naphthyl)-4-phenyl-5-thiazoleacetic acid, m.p. 171—2°C.
4-hydroxy-2-(*p*-methoxyphenyl)-4-2 napthyl-2-thiazoline-5-acetic acid	2-(*p*-methoxyphenyl)-4-(2-naphthyl)-5-thiazoleacetic acid, m.p. 160—2°C.
2-(*p*-chlorophenyl)-4-hydroxy-4-phenyl-2-thiazoline-5-propionic acid	2-(*p*-chlorophenyl)-4-phenyl-5-thiazole-propionic acid, m.p. 177—8°C.
4-hydroxy-4-(1-naphthyl)-2-phenyl-2-2-thiazoline-5-acetic acid.	4-(1-naphthyl)-2-phenyl-5-thiazoleacetic acid, m.p. 166—7°C.
4-hydroxy-4-(2-naphthyl)-2-phenyl-2-thiazoline-5-acetic acid	4-(2-naphthyl)-2-phenyl-5-thiazoleacetic acid, m.p. 168—9°C.
4-hydroxy-2,4-diphenyl-2-thiazoline-5-acetic acid	2,4-diphenyl-5-thiazoleacetic acid, m.p. 152—3°C.
4-hydroxy-4-(*p*-methoxyphenyl)-2-phenyl-2-thiazoline-5-acetic acid	4-(*p*-methoxyphenyl)-2-phenyl-5-thiazole-acetic acid, m.p. 178.5—179.5°C.
4-hydroxy-α-methyl-2,4-diphenylphenyl-2-thiazoline-5-acetic acid	α-methyl-2,4-diphenyl-5-thiazoleacetic acid, m.p. 142—4°C.
4-hydroxy-2-phenyl-4-(2'-thienyl)-2-thiazoline-5-acetic acid	2-phenyl-4-(2'-thienyl)-5-thiazoleacetic acid, m.p. 134.5—135.0°C.
4-hydroxy-2-phenyl-4-(*p*-tolyl)-2-thiazoline 5-acetic acid	2-phenyl-4-(*p*-tolyl)-5-thiazoleacetic acid, m.p. 168—9°C.
4-hydroxy-2-(*p*-methoxyphenyl)-4-phenyl-2-thiazoline-5-propionic acid	2-(*p*-methoxyphenyl)-4-phenyl-5-thiazole-propionic acid, m.p. 174—5°C.
4-hydroxy-4-phenyl-2-(*o*-tolyl)-2-thiazoline-5-propionic acid	4-phenyl-2-(*o*-tolyl)-5-thiazole-propionic acid, m.p. 107—9°C.
4-hydroxy-2,4-diphenyl-2-thiazoline-5-propionic acid	2,4-diphenyl-5-thiazolepropionic acid, m.p. 150°C.
4-hydroxy-2-(*o*-methoxyphenyl)-4-phenyl-2-thiazoline-5-acetic acid	2-(*o*-methoxyphenyl)-4-phenyl-5-thiazole-acetic acid, m.p. 179—180.5°C.

EXAMPLE 6.

Repeating the procedure of Example 4, the following 4 - hydroxy - 2 - thiazoline - 5-alkanoic acids (V) are prepared, which are then dehydrated to afford the following 5-thiazole-alkanoic acids (VI):

(V)  $\xrightarrow{-H_2O}$  (VI)

wherein R^1, R^2 and R^3 are defined as follows:

R^1	R^2	R^3
p-ethylphenyl	phenyl	$HO_2C.CH_2.CH_2$—
p-trifluoromethylphenyl	phenyl	$HO_2C.CH_2.CH(CH_3)$—
phenyl	furyl	$HO_2C.CH_2$—
p-ethoxyphenyl	*p*-ethoxyphenyl	$HO_2C.CH_2$—
phenyl	*p*-iodophenyl	$HO_2C.CH(CH_3).CH(CH_3)$—
p-butylphenyl	*m*-bromophenyl	$HO_2C.CH_2$—
p-nitrophenyl	phenyl	$HO_2C.CH_2$—
phenyl	*p*-fluorophenyl	$HO_2C.CH(C_2H_5)$—
p-iodophenyl	phenyl	$HO_2C.CH_2$—
phenyl	*p*-propylphenyl	$HO_2C.CH_2$—
phenyl	*m*-butylphenyl	$HO_2C.CH_2$—
phenyl	*p*-nitrophenyl	$HO_2C.CH_2$—

EXAMPLE 7.

Ethyl 4-hydroxy-2-phenyl-2-Thiazolin-4-acetate hydrobromide

Ethyl 4-bromo-3-oxybutyrate (5 g.) in acetone (10 ml.) is added to thiobenzamide (3.3 g.) in acetone (50 ml.). After 16 hours at room temperature, the required hydrobromide salt is filtered off (2.0 g., 24%) m.p. 77—78°C.

Analysis: Found: C, 44.8; H, 4.8; N, 4.0. $C_{13}H_{16}BrNO_3S$ requires C, 45.1; H, 4.7; N, 4.0%.

In a similar manner, the following thioamides gives the hydrobromide product indicated, using the above-named ester reactant.

Thioamide	Product
Cyclohexyl thiocarboxamide	Ethyl 4-hydroxy-2-cyclohexyl-2-thiazolin-4-acetate
p-Bromothiobenzamide	Ethyl 4-hydroxy-2-(*p*-bromophenyl)-2-thiazolin-4-acetate
p-Chlorothiobenzamide	Ethyl 4-hydroxy-2-(*p*-chlorophenyl)-2-thiazolin-4-acetate
p-Fluorothiobenzamide	Ethyl 4-hydroxy-2-(*p*-fluorophenyl)-2-thiazolin-4-acetate
m-Trifluoromethylthiobenzamide	Ethyl 4-hydroxy-2-(*m*-trifluoromethylphenyl)-2-thiazolin-4-acetate
(*o*, *m*- or *p*-) Methylthiobenzamide	Ethyl 4-hydroxy-2-(*o*,- *m*- or *p*-tolyl)-2-thiazolin-4-acetate
p-Nitrophenylthiobenzamide	Ethyl 4-hydroxy-2-(*p*-nitrophenyl-2-thiazolin-4-acetate.

EXAMPLE 8.

Ethyl 2,5-diphenyl-4-hydroxy-2-thiazolin-4-acetate

A mixture of ethyl 4-bromo-3-oxo-4-phenylbutyrate (7.12 g.), thiobenzamide (3.4 g.) and anhydrous sodium carbonate (1.2 g.) in ethanol (50 ml. 95%) is stirred at 60—70° for 5 hours. The mixture is then evaporated, and the organic material taken up in ether. The ether solution is washed with water, 2N hydrochloric acid, water, dried ($MgSO_4$) and evaporated to give an oil (6.0 g.) which is chromatographed on alumina. Elution with benzene gives the desired ester as a crystalline white solid (1.8 g., 21%) m.p. 90—91°C.

Analysis: Found: C, 66.8; H, 5.5; N, 4.1; S, 9.6. $C_{19}H_{19}NO_3S$ requires C, 67.0; H, 5.3; N, 4.1; S, 9.4%.

In a similar manner, the following reactants give the products indicated:

Ester	Thioamide	Product
Methyl 4-bromo-3-oxo-4-(*p*-methoxyphenyl)butyrate	Thiobenzamide	Methyl 4-hydroxy-5-(*p*-methoxyphenyl)-2-phenyl-2-thiazolin-4-acetate
Ethyl 4-Bromo-4-(*p*-chlorophenyl)-3-oxobutyrate	Thiobenzamide	Ethyl 4-hydroxy-5-(*p*-chlorophenyl)-2-phenyl-2-thiazolin-4-acetate
Ethyl 4-Bromo-3-oxo-4-phenyl butyrate	*p*-Methoxythiobenzamide	Ethyl 4-hydroxy-2-(*p*-methoxyphenyl)-5-phenyl-2-thiazolin-4-acetic acid
Ethyl 5-Bromo-4-oxo-5-phenylpentanoate	Thiobenzamide	Ethyl 2,5-diphenyl-4-hydroxy-2-thiazolin-4-propionate
Ethyl 4-bromo-3-oxo-4-(1'-naphthyl)butyrate	Thiobenzamide	Ethyl 4-hydroxy-5-(1'-naphthyl)-2-phenyl-2-thiazolin-4-acetate
Ethyl 4-bromo-3-oxo-4-4-phenyl butyrate	*p*-Chloro-thiobenzamide	Ethyl 2-(*p*-chlorophenyl)-4-hydroxy-5-phenyl-2-thiazolin-4-acetate

EXAMPLE 9.

4 - *p* - Chlorophenyl - 4 - hydroxy - 2-phenyl - 2 - thiazolin - 5 - acetic acid

A stirred mixture of 3-bromo-4-*p*-chlorophenyl-4-oxo-butyric acid (400 g.), thiobenzamide (188 g.) and sodium carbonate (73.0 g.) in isopropyl alcohol (1 litre) is heated at 60°C for 1 hour and is then poured into water. The precipitated yellow solid is filtered off, washed with acetone and dried to give 325 g. of the title compound, m.p. 141—142°C. The analytical sample is recrystallised from isopropyl alcohol.

Analysis: Found: C, 58.7; H, 4.1; N, 3.9. $C_{17}H_{14}ClNO_3S$ requires C, 58.7; H, 4.1; N, 4.0%.

EXAMPLE 10.

Ethyl 2 - cyclohexyl - 4 - hydroxy - 4-methyl - 2 - thiazolin - 5 - acetate

A solution of cyclohexyl thiocarboxamide (7.15 g., 0.05 mol.) in acetone (25 ml.) is added to a solution of ethyl β-acetyl-β-bromo-propionate (11.15 g., 0.05 mol.) in acetone (25 ml.) and the mixture is kept at room temperature for 0.5 hours and then at 0°C for 3 hours. The white crystalline material is filtered off, washed with acetone and dried to give 6.84 g. (37.6%) of the thiazoline ester as its hydrobromide, m.p. 117—118°C.

Analysis: Found: C, 45.9; H, 6.7; N, 3.8. $C_{14}H_{23}NO_3S.HBr$ requires C, 46.1; H, 6.7; N, 3.9%.

EXAMPLE 11.

2 - Cyclohexyl - 4 - hydroxy - 4 - methyl - 2-thiazolin-5-acetic acid

The reaction of cyclohexyl thiocarboxamide (7.15 g., 0.05 mol.) and β-acetyl-β-bromopropionic acid (9.75 g., 0.05 mol.) according to the method of Example 10 gives 10.16 g. (60.5%) of the required thiazoline acid as its hydrobromide, m.p. 129—130°C.

Analysis: Found: C, 43.1; H, 6.0; N, 4.5. $C_{12}H_{19}NO_3S.HBr$ requires C, 42.8; H, 6.0; N, 4.2%.

EXAMPLE 12.

Ethyl 4-hydroxy-2-cyclohexyl-2-thiazolin-4-acetate

The reaction of cyclohexyl thiocarboxamide (7.15 g., 0.05 mol.) and ethyl 4-bromoacetoacetate (10.41 g., 0.05 mol.) by the method of Example 10 affords 11.0 g. (62.5%) of the title compound as its hydrobromide, m.p. 124—125°C.

Analysis: Found: C, 44.5; H, 6.3; N, 4.05. $C_{13}H_{21}NO_3S.HBr$ requires C, 44.3; H, 6.3; N, 4.0%.

EXAMPLE 13.

Ethyl 2-p-chlorophenyl-4-hydroxy-2-thiazolin-4-acetate

A solution of *p*-chlorothiobenzamide (8.59 g., 0.05 mol.) in acetone (40 ml.) is added to a solution of ethyl 4-bromoacetoacetate (10.41 g., 0.05 mol.) in acetone and the mixture is allowed to stand at room temperature for 21 hours. The crystalline material, after filtering off and washing with ice-cold acetone and ice-cold ether and drying, affords the title compound (8.05 g., 42.3%) as its hydrobromide, m.p. 97—98°C.

Analysis: Found: C, 41.0; II, 3.8; N, 3.5. $C_{13}H_{14}ClNO_3S.HBr$ requires C, 41.0; H, 4.0; N, 3.7%.

The hydrobromide, on treating with sodium hydrogen carbonate, gives a 72.8% yield of the free base, m.p. 109—110°C. after recrystallising from ether.

Analysis: Found: C, 52.1; H, 4.6; N, 4.6. $C_{13}H_{14}ClNO_3S$ requires C, 52.1; H, 4.7; N, 4.7%.

EXAMPLE 14.

4-Hydroxy-2-(*p*-chloro-phenyl)-2-thiazoline-4-propionic acid

The reaction of *p*-chlorothiobenzamide and 5-bromo-laevulinic acid by the method of Example 10 affords the title compound.

In the preparation of 4-hydroxy-thiazoline-4-acetic acids, the γ-haloacetoacetic acid is, of course, protected in conventional manner to prevent decarboxylation, and after the cyclisation reaction the protecting group is conventionally removed; for instance a benzyl ester which is removed by catalytic hydrogenation.

EXAMPLE 15.

2-(*p*-Chlorophenyl)-4-hydroxy-2-thiazoline-4-acetic acid

The reaction of benzyl 4-bromoacetoacetate and *p*-chlorothiobenzamide affords benzyl 2-(p - chlorophenyl) - 4 - hydroxy - 2 - thiazoline-4-acetate which is subsequently hydrogenated in tetrahydrofuran in the presence of an equal weight of 10% palladium-on-charcoal catalyst to give the title compound.

The new and novel compounds of the present invention in standard pharmacological test procedures generally demonstrate an ability to reduce inflammation and are useful as agents for the treatment of inflammation.

In the pharmacological evaluation of the properties of the compounds of this invention, the effects *in vivo* of the compounds are tested in the procedure of Winter *et al* and Buttle *et al* specified above.

The compounds of general formula I when administered orally in the above test procedure at a dosage of 10 to 250 mg./kg. depending on the compound in question, generally demonstrated anti-inflammatory activity. Good activity was obtained with 4-(*p*-chlorophenyl)-4-hydroxy - 2 - phenyl - 2 - thiazoline - 5 - acetic acid with 4-(*p*-bromophenyl)-4-hydroxy-2-phenyl-2-thiazoline-5-acetic acid and with ethyl 2 - (*p* - chlorophenyl) - 4 - hydroxy - 2-thiazoline-4-acetate, as shown in the following table, which shows the % inhibition and dosage tested and also the LD_{50} tested orally on mice.

Compound	Dose mg./kg.	% inhibition	LD_{50} (mice) mg./kg.
4-(*p*-Chlorophenyl)-4-hydroxy-2-phenyl-2-thiazoline-5-acetic acid	30	61	>2000
4-(*p*-Bromophenyl)-4-hydroxy-2-phenyl-2-thiazoline-5-acetic acid	25	51	> 400
Ethyl 2-*p*-chlorophenyl-4-hydroxy 2-thiazoline-4-acetate	100	53	

EXAMPLE 16.

2-Phenyl-4-*p*-chlorophenyl-4-hydroxy-thiazoline-5-acetic acid	125 mg.
Lactose	120 mg.
Magnesium stearate	5 mg.

Capsules of the above were made up by thoroughly mixing together batches of the above ingredients and filling hard gelatine capsules (250 mg.) with the mixture.

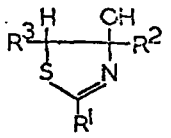
EXAMPLE 17.

2-Phenyl-4-*p*-bromophenyl-4-hydroxy-thiazoline-5-acetic acid	125 mg.
Lactose	100 mg.
Avicel (Registered Trade Mark)	30 mg.
Dried Maize Starch	40 mg.
Magnesium stearate	5 mg.

Tablets of the above composition were made by milling the active ingredient to 40 mesh (British Standard), sieving through a 40 mesh (British Standard) sieve, mixing the milled material with the other components and compressing to form tablets.

WHAT WE CLAIM IS:—

1. A thiazoline of the general formula



and acid addition salts thereof, in which R^1 is a substituted or unsubstituted aryl radical (which may be a heteroaryl radical) or a cycloalkyl radical, R^2 is a carboxyalkyl radical containing 2 to 6 carbon atoms or an ester, nitrile or amide derivative thereof, R^3 is hydrogen, lower alkyl or a substituted or unsubstituted aryl radical (which may be a heteroaryl radical) and either the 4- or the 5- position contains the radical R^2, the remaining one of the 4- and 5- positions containing the radical R^3.

2. A thiazoline according to Claim 1 in which R^1 and R^3 are substituted or unsubstituted aryl radicals (which may be a heteroaryl radicals) and the group R^2 is in the 5-position.

3. A thiazoline according to Claim 2 in which R^3 is phenyl, halophenyl, trifluoromethylphenyl or nitrophenyl.

4. A thiazoline according to Claim 2, in which R^1 is phenyl and R^3 is halophenyl or trifluoromethylphenyl and R^2 is a carboxymethyl radical.

5. A thiazoline according to Claim 2 in which R^1 is halophenyl or trifluoromethylphenyl and R^3 is halophenyl or trifluoromethylphenyl and R^2 is a carboxymethyl radical.

6. A thiazoline according to Claim 1 in which R^3 is hydrogen or lower alkyl and R^2 is in the 4-position.

7. 4 - (*p* - Bromophenyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid.

8. 4 - (*p* - Chlorophenyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid.

9. 4 - (*p* - Fluorophenyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid.

10. 4 - (*m* - Trifluoromethylphenyl) - 4-hydroxy-2-phenyl-2-thiazoline-5-acetic acid.

11. 4 - (*p* - Trifluoromethylphenyl) - 4-hydroxy-2-phenyl-2-thiazoline-5-acetic acid.

12. 4 - (3' - Furyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-propionic acid.

13. 4 - (2 - Thienyl) - 4 - hydroxy - 2 - (*o*-tolyl)-2-thiazoline-5-acetic acid.

14. 4 - (*p* - Methoxyphenyl) - 4 - hydroxy-2-(*p*-chlorophenyl)-2-thiazoline-5-acetic acid.

15. 4 - Phenyl - 4 - hydroxy - 2 - (*p*-chlorophenyl)-2-thiazoline-5-acetic acid.

16. 4 - (2 - Thienyl) - 4 - hydroxy - 2 - (*p*-chlorophenyl)-2-thiazoline-5-acetic acid.

17. 2,4 - Bis(*p* - methoxyphenyl) - 4-hydroxy-2-thiazoline-5-acetic acid.

18. 4 - (*p* - Methoxyphenyl) - 4 - hydroxy-2-(*o*-tolyl)-2-thiazoline-5-acetic acid..

19. 4 - Phenyl - 4 - hydroxy - 2 - (*o* - tolyl)-2-thiazoline-5-acetic acid.

20. 4 - Phenyl - 4 - hydroxy - 2 - (*m*-tolyl)-2-thiazoline-5-acetic acid.

21. 4 - Phenyl - 4 - hydroxy - 2 - (*p*-methoxyphenyl)-2-thiazoline-5-acetic acid.

22. 4 - Phenyl - 4 - hydroxy - 2 - (*o*-chlorophenyl)-2-thiazoline-5-acetic acid.

23. 4 - Phenyl - 4 - hydroxy - 2 - (*p* - tolyl)-2-thiazoline-5-acetic acid.

24. 4 - Phenyl - 4 - hydroxy - 2 - (1-naphthyl)-2-thiazoline-5-acetic acid.

Compound	Dose mg./kg.	% inhibition	LD_{50} (mice) mg./kg.
4-(*p*-Chlorophenyl)-4-hydroxy-2-phenyl-2-thiazoline-5-acetic acid	30	61	>2000
4-(*p*-Bromophenyl)-4-hydroxy-2-phenyl-2-thiazoline-5-acetic acid	25	51	> 400
Ethyl 2-*p*-chlorophenyl-4-hydroxy 2-thiazoline-4-acetate	100	53	

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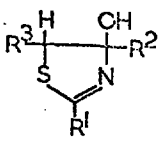
EXAMPLE 17.

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WHAT WE CLAIM IS:—

1. A thiazoline of the general formula



and acid addition salts thereof, in which R^1 is a substituted or unsubstituted aryl radical (which may be a heteroaryl radical) or a cycloalkyl radical, R^2 is a carboxyalkyl radical containing 2 to 6 carbon atoms or an ester, nitrile or amide derivative thereof, R^3 is hydrogen, lower alkyl or a substituted or unsubstituted aryl radical (which may be a heteroaryl radical) and either the 4- or the 5- position contains the radical R^2, the remaining one of the 4- and 5- positions containing the radical R^3.

2. A thiazoline according to Claim 1 in which R^1 and R^3 are substituted or unsubstituted aryl radicals (which may be a heteroaryl radicals) and the group R^2 is in the 5-position.

3. A thiazoline according to Claim 2 in which R^3 is phenyl, halophenyl, trifluoromethylphenyl or nitrophenyl.

4. A thiazoline according to Claim 2, in which R^1 is phenyl and R^3 is halophenyl or trifluoromethylphenyl and R^2 is a carboxymethyl radical.

5. A thiazoline according to Claim 2 in which R^1 is halophenyl or trifluoromethylphenyl and R^3 is halophenyl or trifluoromethylphenyl and R^2 is a carboxymethyl radical.

6. A thiazoline according to Claim 1 in which R^3 is hydrogen or lower alkyl and R^2 is in the 4-position.

7. 4 - (*p* - Bromophenyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid.

8. 4 - (*p* - Chlorophenyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid.

9. 4 - (*p* - Fluorophenyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid.

10. 4 - (*m* - Trifluoromethylphenyl) - 4-hydroxy-2-phenyl-2-thiazoline-5-acetic acid.

11. 4 - (*p* - Trifluoromethylphenyl) - 4-hydroxy-2-phenyl-2-thiazoline-5-acetic acid.

12. 4 - (3′ - Furyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-propionic acid.

13. 4 - (2 - Thienyl) - 4 - hydroxy - 2 - (*o*-tolyl)-2-thiazoline-5-acetic acid.

14. 4 - (*p* - Methoxyphenyl) - 4 - hydroxy-2-(*p*-chlorophenyl)-2-thiazoline-5-acetic acid.

15. 4 - Phenyl - 4 - hydroxy - 2 - (*p*-chlorophenyl)-2-thiazoline-5-acetic acid.

16. 4 - (2 - Thienyl) - 4 - hydroxy - 2 - (*p*-chlorophenyl)-2-thiazoline-5-acetic acid.

17. 2,4 - Bis(*p* - methoxyphenyl) - 4-hydroxy-2-thiazoline-5-acetic acid.

18. 4 - (*p* - Methoxyphenyl) - 4 - hydroxy-2-(*o*-tolyl)-2-thiazoline-5-acetic acid..

19. 4 - Phenyl - 4 - hydroxy - 2 - (*o* - tolyl)-2-thiazoline-5-acetic acid.

20. 4 - Phenyl - 4 - hydroxy - 2 - (*m*-tolyl)-2-thiazoline-5-acetic acid.

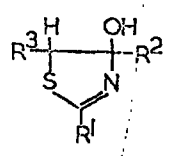
21. 4 - Phenyl - 4 - hydroxy - 2 - (*p*-methoxyphenyl)-2-thiazoline-5-acetic acid.

22. 4 - Phenyl - 4 - hydroxy - 2 - (*o*-chlorophenyl)-2-thiazoline-5-acetic acid.

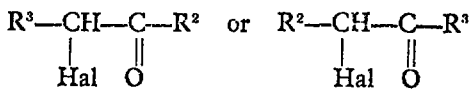
23. 4 - Phenyl - 4 - hydroxy - 2 - (*p* - tolyl)-2-thiazoline-5-acetic acid.

24. 4 - Phenyl - 4 - hydroxy - 2 - (1-naphthyl)-2-thiazoline-5-acetic acid.

25. 4 - Phenyl - 4- hydroxy - 2 - (*m* - trifluoromethylphenyl)-2-thiazoline-5-acetic acid.
26. 4 - (2 - Thienyl) - 4 - hydroxy - 2 - (*p*-methoxyphenyl)-2-thiazoline-5-acetic acid.
27. 4 - Phenyl - 4 - hydroxy - 2 - (2-naphthyl)-2-thiazoline-5-acetic acid.
28. 4 - (2 - Naphthyl) - 4 - hydroxy - 2-(*p*-methoxyphenyl)-2-thiazoline-5-acetic acid.
29. 4 - Phenyl - 4 - hydroxy - 2 - (*p*-chlorophenyl)-2-thiazoline-5-propionic acid.
30. 4 - (1 - Naphthyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid.
31. 4 - (2 - Naphthyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid.
32. 2,4 - Diphenyl - 4 - hydroxy - 2 - thiazoline-5-acetic acid.
33. 4 - (*p* - Methoxyphenyl) - 4 - hydroxy-2-phenyl-2-thiazoline-5-acetic acid.
34. 2,4 - Diphenyl - 4 - hydroxy - 2 - thiazoline-5-(*α*-methyl)acetic acid.
35. 4 - (2′ - Thienyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid.
36. 4 - (*p* - Tolyl) - 4 -hydroxy - 2 - phenyl-2-thiazoline-5-acetic acid.
37. 4 - Phenyl - 4 - hydroxy - 2 - (*p*-methoxyphenyl)-2-thiazoline-5-propionic acid.
38. 4 - Phenyl - 4 - hydroxy - 2 -(*o* - tolyl)-2-thiazoline-5-propionic acid.
39. 2,4 - Diphenyl - 4 - hydroxy - 2 - thiazoline-5-propionic acid.
40. 4 - Phenyl - 4 - hydroxy - 2 - (*o*-methoxyphenyl)-2-thiazoline-5-acetic acid.
41. 4 - Phenyl - 4 - hydroxy - 2 - (*p* - ethylphenyl)-2-thiazoline-5-propionic acid.
42. 4 - Phenyl - 4 - hydroxy - 2 - (*p* - trifluoromethylphenyl) - 2 - thiazoline - 5 - (*α*-methyl)acetic acid.
43. 4 - Furyl - 4 - hydroxy - 2 - phenyl - 2-thiazoline-5-acetic acid.
44. 2,4 - Bis(*p* - ethoxyphenyl) - 4 - hydroxy-2-thiazoline-5-acetic acid.
45. 4 - (*p* - Iodophenyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-(*α*,*β*-dimethyl) propionic acid.
46. 4 - (*m* - Bromophenyl) - 4 - hydroxy-2 - (*p* - butylphenyl) - 2 - thiazoline - 5-acetic acid.
47. 4 - Phenyl - 4 - hydroxy - 2 - (*p*-nitrophenyl)-2-thiazoline-5-acetic acid.
48. 4 - (*p* - Fluorophenyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-(*α*-ethyl)acetic acid.
49. 4 - Phenyl - 4 - hydroxy - 2 - (*p* - iodophenyl)-2-thiazoline-5-acetic acid.
50. 4 - (*p* - Propylphenyl) - 4 - hydroxy-2-phenyl-2-thiazoline-5-acetic acid.
51. 4 - (*m* - Butylphenyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid.
52. 4 - (*p* - Nitrophenyl) - 4 - hydroxy - 2-phenyl-2-thiazoline-5-acetic acid.
53. Ethyl 2-phenyl-4-hydroxy-2-thiazoline-4-acetate.
54. Ethyl 2-cyclohexyl-4-hydroxy-2-thiazoline-4-acetate.
55. Ethyl 2-(*p*-bromophenyl)-4-hydroxy-2-thiazoline-4-acetate.
56. Ethyl 2-(*p*-chlorophenyl)-4-hydroxy-2-thiazoline-4-acetate.
57. Ethyl 2-(*p*-fluorophenyl)-4-hydroxy-2-thiazoline-4-acetate.
58. Ethyl 2-(*m*-trifluoromethylphenyl)-4-hydroxy-2-thiazoline-4-acetate.
59. Ethyl 2-(*o*-tolyl)-4-hydroxy-2-thiazoline-4-acetate.
60. Ethyl 2-(*m*-tolyl)-4-hydroxy-2-thiazoline-4-acetate.
61. Ethyl 2 - (*p* - tolyl) - 4 - hydroxy - 2-thiazoline-4-acetate.
62. Ethyl 2 - (*p* - nitrophenyl) - 4 - hydroxy-2-thiazoline-4-acetate.
63. Ethyl 2,5 - diphenyl - 4 - hydroxy - 2-thiazoline-4-acetate.
64. Methyl 5-(*p*-methoxyphenyl)-4-hydroxy-2-phenyl-2-thiazoline-4-acetate.
65. Ethyl 5-(*p*-chlorophenyl)-4-hydroxy-2-phenyl-2-thiazoline-4-acetate.
66. Ethyl 5 - phenyl - 4 - hydroxy - 2 - (*p*-methoxyphenyl)-2-thiazoline-4-acetate.
67. Ethyl 2,5 - diphenyl - 4 - hydroxy - 2-thiazoline-4-propionate.
68. Ethyl 5 - (1′ - naphthyl) - 4 - hydroxy-2-phenyl-2-thiazoline-4-acetate.
69. Ethyl 5 - phenyl - 4 - hydroxy - 2 - (*p*-chlorophenyl)-2-thiazoline-4-acetate.
70. Ethyl 2 - cyclohexyl - 4 - hydroxy - 4-methyl-2-thiazoline-5-acetate.
71. 2 - Cyclohexyl - 4 - hydroxy - 4-methyl-2-thiazoline-5-acetic acid.
72. Ethyl - 4 - hydroxy - 2 - cyclohexyl - 2-thiazoline-4-acetate.
73. Ethyl 2-(*p*-chlorophenyl)-4-hydroxy-2-thiazoline-4-acetate.
74. A 4-hydroxy-thiazoline-4 or 5-alkanoic acid or ester substantially as described herein and shown with reference to the Examples.
75. A process for the preparation of a thiazoline of general formula

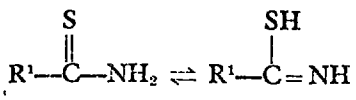


and acid addition salts thereof, in which R^1 is a substituted or unsubstituted aryl radical (which may be a heteroaryl radical) or a cycloalkyl radical, R^2 is a carboxyalkyl radical containing 2 to 6 carbon atoms or an ester, nitrile or amide derivative thereof, R^3 is hydrogen, lower alkyl or a substituted or unsubstituted aryl radical (which may be a heteroaryl radical) and either the 4- or the 5- position contains the radical R^2, the remaining one of the 4- and 5- positions containing the radical R^3; in which a compound of the general formula



or

is reacted with a thioamide of the general formula



(where R^1, R^2 and R^3 have the meanings defined above and Hal is a halogen atom) under mild conditions below the dehydration temperature of the thiazoline hydrohalide thus produced and, if desired, treated with a base to give the thiazoline free base, and if desired, treated with an acid to form an acid addition salt thereof.

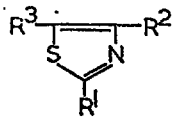
76. A process according to Claim 75 when carried out at temperatures up to 80°C in an inert organic solvent in which the thiazoline hydrohalide formed is insoluble.

77. A process according to Claim 75 when carried out in isopropanol in the presence of an alkali metal carbonate to give the thiazoline free base.

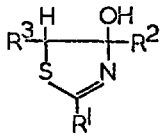
78. A process for the preparation of a 4-hydroxy-thiazoline compound substantially as described herein and shown with reference to any one of the Examples.

79. A 4-hydroxy-thiazoline prepared by a process according to any one of Claims 75 to 77.

80. A process for the preparation of a thiazole of general formula



in which R^1 is a substituted or unsubstituted aryl radical (which may be a heteroaryl radical) or a cycloalkyl radical, R^2 is a carboxyalkyl radical containing 2 to 6 carbon atoms or an ester, nitrile or amide derivative thereof, R^3 is hydrogen, lower alkyl or a substituted or unsubstituted aryl radical (which can be a heteroaryl radical) and either the 4- or the 5- position contains the radical R^2, the remaining one of the 4- and 5- positions containing the radical R^3; in which a corresponding 4-hydroxy-thiazoline of general formula



or an acid addition salt thereof, in which R^1, R^2 and R^3 have the above defined meanings is dehydrated by heating to above the dehydration temperature, if desired in the presence of an acid.

81. A process according to Claim 80 substantially as described herein and shown with particular reference to any one of Examples 2 to 6.

82. A thiazole prepared by a process according to either Claim 80 or Claim 81.

83. A pharmaceutical composition comprising a thiazole according to Claim 82 and a pharmaceutically acceptable carrier.

84. A pharmaceutical composition comprising a 4-hydroxy-thiazoline according to any one of Claims 1 to 10, 53 to 69 and 79 and a pharmaceutically acceptable carrier.

85. A pharmaceutical composition comprising a 4-hydroxy-thiazoline according to any one of Claims 11 to 52 and 70 to 74 and a pharmaceutically acceptable carrier.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1972.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

