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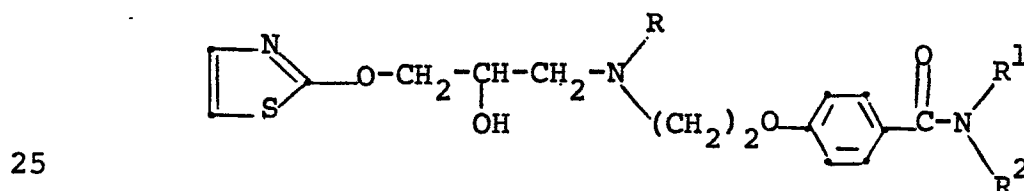
TITLE OF THE INVENTION

NOVEL DI-AND TRI- SUBSTITUTED THIAZOLES

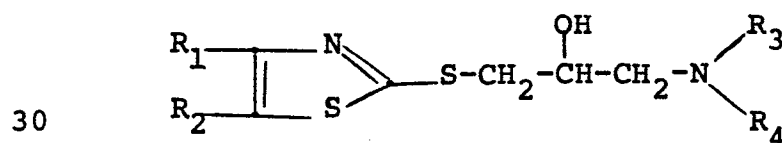
BACKGROUND OF THE INVENTION

The present invention involves novel di-
 5 and tri- substituted thiazoles having pharmaceutical
 activity as β -adrenergic blocking agent.

Thiazoles having an aminohydroxypropoxy
 substituent in the 2-position with or without a
 specific additional substituent in the 4 or 5-
 10 position, are known and are taught to have β -
 adrenergic stimulating activity (U.S. 3,850,945).
 Thiazoles having an aminohydroxypropoxy substituent
 in the 4 or 5-position with no additional substitu-
 tion are also known and are taught to have β -
 15 adrenergic stimulating activity (U.S. 3,850,947,
 U.S. 3,850,946). Thiazoles having the aminohydroxy-
 propoxy substituent in the 2-position with an amino-
 carbonyl, formamido, substituted oxycarbonyl amino
 group in the 4 or 5-position, are known and taught
 20 to have β -adrenergic blocking activity (U.S. 3,897,411).
 Thiazoles having the following formula



are known and are taught to be β -adrenergic blocking
 agents. (U.S. 3,897,442). Thiazoles of the formula



are known and are taught to block β -adrenergic receptors (U.S. 3,932,400).

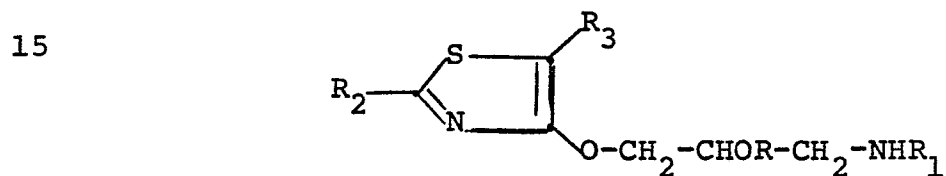
Novel di- and tri-substituted thiazoles having a 4(3-amino-2-OR-propoxy) substituent have been discovered. The thiazoles are active as β -adrenergic blocking agents.

Summary of the Invention

Di- and tri- substituted thiazoles having a 4(3-amino-2-OR-propoxy) group and their pharmaceutical use.

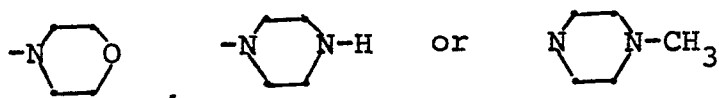
Description of the Preferred Embodiments

An embodiment of the present invention is compounds having the formula



and pharmaceutically acceptable salts thereof wherein

- 20
- R is hydrogen or C_2-C_{12} acyl,
- R_1 is C_1-C_{12} alkyl,
- R_2 is hydrogen, CF_3 , C_6-C_{12} carbocyclic aryl, 6-membered-N-heteroaryl, C_1-C_6 alkyl, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, thienyl,
- 25 and furfuryl,
- R_3 is C_1-C_6 alkyl, $-COOC_1-C_6$ alkyl, $COOC_6-C_{12}$ aryl, cyano, C_6-C_{12} carbocyclic aryl, CF_3 or $-C(=O)NR_4R_5$ wherein R_4 and R_5 are independently selected
- 30 from H and C_1-C_6 alkyl or are joined forming



provided that when R_2 is phenyl, R_3 is other than C_1-C_6 alkyl or $COOC_1-C_6$ alkyl.

5 The pharmaceutically acceptable salts are the acid addition salts of the formula I free base. Suitable acids include organic as well as inorganic acids. Examples of useful organic acids are carboxylic acids such as acetic acid, pamoic acid, maleic acid, succinic acid, citric acid, tartaric
10 acid, oxalic acid, malic acid, pivalic acid, heptanoic acid, lauric acid, propanoic acid, pelargonic acid, oleic acid and the like, and non-carboxylic acids such as isethionic acid. Examples of useful
15 inorganic acids are the hydrogen halides i.e., HCl, HBr, HI, phosphoric acid, sulfuric acid, and the like. The hydrohalide salts especially the hydrochlorides and maleic acids, especially the hydrogen maleate, are preferred.

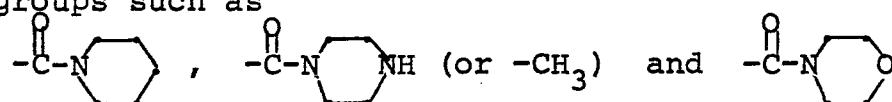
R may be hydrogen or C_2-C_{12} acyl. The
20 C_2-C_{12} acyl groups include alkanoyl groups such as acetyl, pivaloyl, dodecanoyl, hexanoyl, succinoyl and the like - and carbocyclic aroyl groups such as benzoyl, 1- or 2- naphthoyl, p-methylbenzoyl, p-phenylbenzoyl and the like. The C_2-C_6 alkanoyl
25 and benzoyl groups are preferred acyl groups. Hydrogen is a most preferred R group.

The R_1 substituent includes C_1-C_{12} alkyl groups and preferably the C_1-C_6 alkyl groups. The alkyl groups are exemplified by methyl, $C_{12}H_{25}$, hexyl,
30 2-ethylhexyl, isopropyl, sec-butyl, heptyl and the like. The C_3-4 branched chain alkyl R_1 groups are more preferred, with t-butyl being a most preferred group.

R_2 includes H, CF_3 , C_6-C_{12} carbocyclic aryl
35 such as phenyl, monosubstituted phenyl e.g. p-tolyl, o-halophenyl, p-nitrophenyl, p-methoxyphenyl and p-halophenyl; indanyl; 1- or 2-naphthyl and the like,

6-membered-N-heteroaryl such as 2-, 3- or 4-pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl and the like; thienyl, furfuryl, C₁-C₆alkyl, e.g. methyl, n-hexyl, isopropyl, sec-butyl, ethyl and the like, C₁-C₆ alkylthio, and the sulfinyl and sulfonyl derivatives exemplified by C₂H₅-S, C₄H₉-SO, C₆H₁₃-SO₂, CH(CH₃)₂, CH₃-SO, t-butyl-S and the like. Preferred R₂ groups are hydrogen, C₁-C₆alkyl and C₁-C₆alkylthio, especially CH₃-S.

The R₃ substituent includes CF₃, C₁-C₆ alkyl, CN, C₆-C₁₂ carbocyclic aryl such as phenyl, carboxylic acid esters and amides. The C₁-C₆ alkyl group is exemplified by CH₃, isopropyl, and the like. The ester group is C₁-C₆ alkylester exemplified by -COOCH₃, -COOC₆H₁₃, -COOCH(CH₃)₂, -COOC₂H₅ and the like and C₆-C₁₂ aryylester, preferably carbocyclic aryl, exemplified by C₆H₅-OOC, p-CH₃-C₆H₄-OOC-, p-C₆H₅-C₆H₄-OOC-, C₉H₉-OOC- and the like. The amide group includes -CONH₂, C₁-C₆ substituted amide groups such as -CON(CH₃)₂, -CON(C₆H₁₃)₂, -CONHC₂H₅, -CON (sec. butyl)₂ and the like and carbonyl heterocyclic groups such as

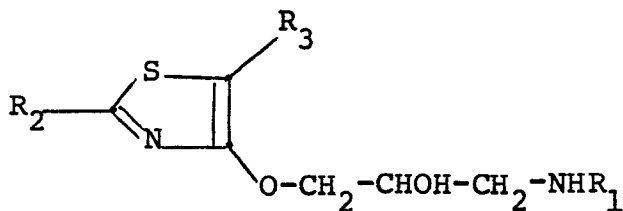


of the R₃ groups, CN, CF₃ and amide, especially CONH₂, are preferred.

The formula I compounds have a chiral center (at the 2 carbon in the propoxy substituent) which confers optical activity. The optical isomers are designated conventionally as L and D, l and d, + and -, S and R or by combinations of these symbols. Where the formula or compound name herein carries no specific designation, the formula or name includes the individual isomers, the mixtures thereof and racemates.

The thiazole compounds which are preferred

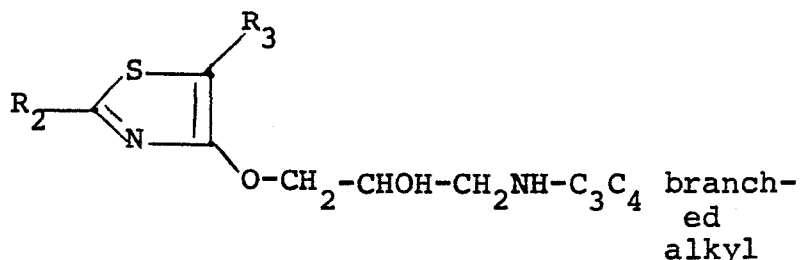
have the formula



(II)

Formula II compounds where R_2 is H, C_1-C_6 alkylthio, preferably CH_3-S- , or said heteroaryl groups, especially pyridyl, R_3 is CN, CF_3 , amide, C_1-C_6 alkyl or said ester group and R_1 is C_1-C_6 alkyl especially C_3-C_4 branched alkyl are more preferred. In most preferred formula II compounds, R_2 is said alkylthio or heteroaryl, R_3 is CN, CF_3 , $CONH_2$, C_1-C_6 alkyl or said ester and R_1 is C_3-C_4 branched alkyl.

Another preferred group of thiazoles has the formula



III

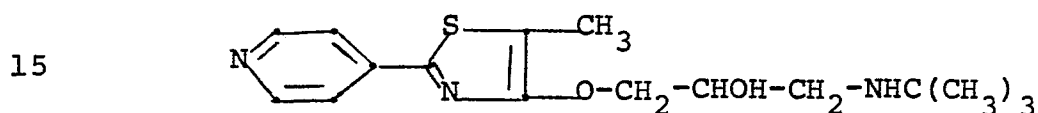
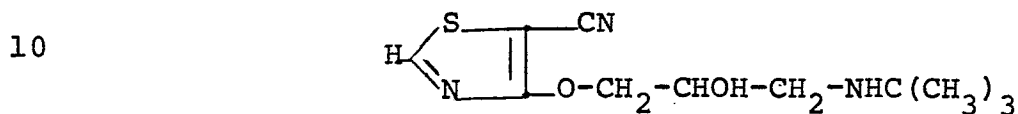
where R_2 is H, C_1-C_6 alkyl, C_1-C_6 alkylthio or pyridyl, R_3 is CN, CF_3 , C_1-C_6 alkyl or $CONH_2$. In more preferred formula III thiazoles, said branched alkyl is tert.-butyl, R_2 is H, CH_3 , CH_3S or pyridyl, and R_3 is CN, CH_3 , $CONH_2$ or CF_3 and the thiazoles where said branched alkyl is tert.-butyl, R_2 is H, CH_3S or pyridyl and R_3 is CN or $CONH_2$ are particularly preferred.

Of the optical isomers those having the S-isomer configuration are preferred.

The thiazoles of the present invention have β -adrenergic blocking activity. This was determined in an in-vivo test using dogs as the test animals. In this test, representative thiazole compounds,

were found to counteract the β -adrenergic stimulating effect of isoproterenol.

Certain of the present thiazoles also exhibit an antihypertensive effect of immediate onset when administered to a spontaneously hypertensive (SH) rat. Representative of such compounds are those having the formula



The present thiazoles also show random vasodilator activity.

The present thiazole compounds will effect β -adrenergic blockade in humans. This β -adrenergic blocking effect is useful in the therapeutic treatment of various cardiovascular conditions such as angina pectoris, arrhythmia etc. In administering these formula I compounds for their β -adrenergic blocking effect, the daily dosage may range from about 1.5 mg. to about 3000 mg. Preferred daily dosages are about 6.5 mg. to about 200 mg. Conventional dosage forms suitable for oral as well as parenteral, e.g. intravenous, intraperitoneal etc., administration are used. Oral dosage forms include tablets, capsules, troches, liquid formulations e.g. solutions, emulsions, elixirs, etc. - parenteral dosage forms include liquid formulations especially solutions. The compositions are prepared using conventional procedures and compounding ingredients such as starch, sterile water, flavoring additives, antioxidants, binders, vegetable oils, sweetening

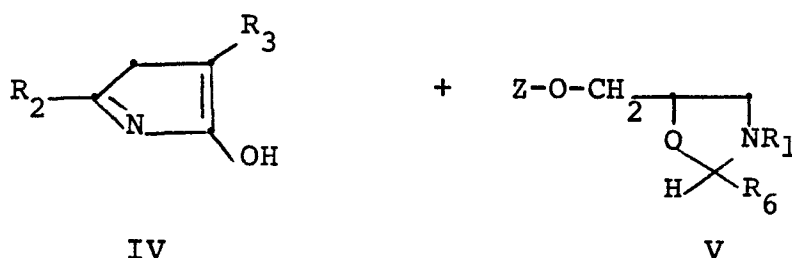
agents, glycerine and the like.

Thiazoles which exhibit the immediate onset antihypertensive activity are useful for treating hypertensive humans at daily dosages ranging from about 100 to about 3000 mg. administered in oral or parenteral dosage forms.

The present thiazoles can be prepared by any convenient process.

One such process involves the coupling of a suitably substituted thiazole with a suitably substituted oxazolidine and hydrolyzing the reaction product obtained. This process is illustrated by the following set of reaction equations:

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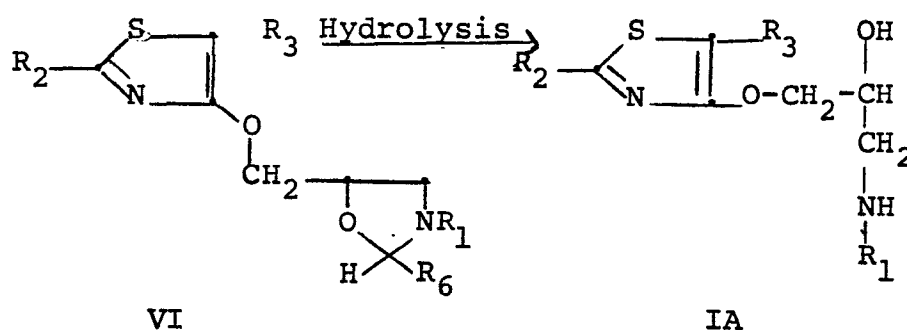


20

IV

Base

25



30

Z is an alkyl or arylsulfonyl group. Examples of sulfonyl groups are $\text{CH}_3\text{-SO}_2\text{-}$, $\text{C}_6\text{H}_5\text{-SO}_2\text{-}$, $\text{NO}_2\text{-C}_6\text{H}_4\text{SO}_2\text{-}$, $\text{p-CH}_3\text{-C}_6\text{H}_4\text{-SO}_2\text{-}$, mesitylene- $\text{SO}_2\text{-}$, $\text{CH}_3\text{O-C}_6\text{H}_4\text{-SO}_2\text{-}$, trichlorobenzene- $\text{SO}_2\text{-}$, $\text{C}_{16}\text{H}_{33}\text{-SO}_2\text{-}$ and the like.

35

Suitable bases are alkali metal bases such as K_2CO_3 , $\text{K-O-C(CH}_3)_3$, NaH , organolithiums e.g. phenyllithium, n-butyllithium, lithium diisopropyl amide and the like.

R_6 is hydrogen or other C_1 - C_{12} alkyl or C_6 - C_{12} carbocyclic aryl residue of any suitable aldehyde $R_6-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}=\text{O}$. Examples of suitable aldehydes are the aryl aldehydes such as benzaldehyde, naphthaldehyde 4-phenylbenzaldehyde, furfural, bromobenzaldehyde, tolualdehyde, mesitaldehyde and the like, or an alkanal such as acetaldehyde, butyraldehyde, $C_{11}H_{13}-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}=\text{O}$ and the like. The process for preparing oxazolidines where Z is hydrogen (and a related coupling reaction) is disclosed in U.S. 3,718,647 and U.S. 3,657,237 and to the extent necessary the pertinent disclosure is incorporated herein by reference.

The coupling reaction can be carried out at temperatures ranging from about 0°C. to about 130°C. A temperature range of about 50°C. to about 130°C is preferred. The reaction is generally carried out in a solvent. Any suitable solvent may be used. Examples of useful solvents are dimethylformamide, dimethylsulfoxide, hexamethylphosphoramide, tert. butanol, dioxane, toluene, acetone and the like. The hydrolysis is carried out using a conventional acid system e.g. by treatment with a solution of any suitable acid such as HCl, H_2SO_4 , CH_3COOH and the like. The hydrolysis product can be directly obtained as the salt of the acid used for the hydrolysis. Ordinarily, the product IA is recovered as the free base after conventional neutralization of the salt.

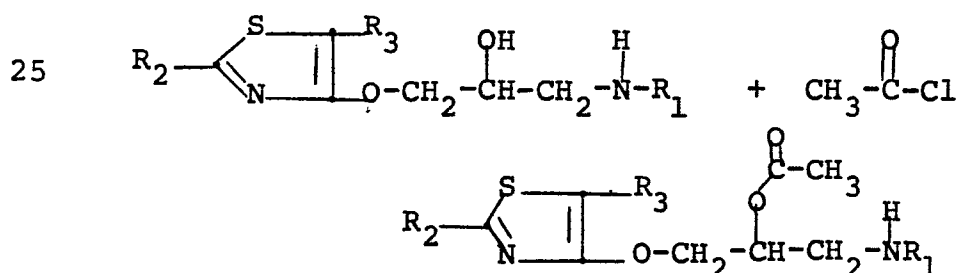
The coupling reaction is ordinarily carried out at atmospheric pressure. Higher pressures may be used if desired.

When a racemic oxazolidine (formula V) is used as a reactant, the product is obtained as a racemate. The racemate may be separated into its individual enantiomers by conventional resolution techniques.

When R_6 in the oxazolidine (e.g. formula V or VI) is other than hydrogen, in addition to the chiral center at oxazolidine position 5 there is a second chiral center at position 2. However, when-
 5 ever an oxazolidine is designated e.g. as (S), (R) or (R,S), this designation refers only to the optical configuration around the carbon atom at the 5 position.

By using a single optical isomer of the
 10 formula V oxazolidine in the above reaction the thiazole product (IA) may be obtained directly as a single enantiomer. This provides a convenient way for directly preparing individual isomers of the present thiazoles.

15 Thiazoles represented by formula I wherein R is other than hydrogen are conveniently prepared by treating the corresponding thiazole where R is hydrogen with an appropriate acylating agent such as an acyl halide, e.g. undecanoyl chloride, pivaloyl
 20 chloride, benzoylchloride, p-methoxybenzoyl chloride, an anhydride e.g. acetic anhydride and the like. The reaction is illustrated by the following equation:

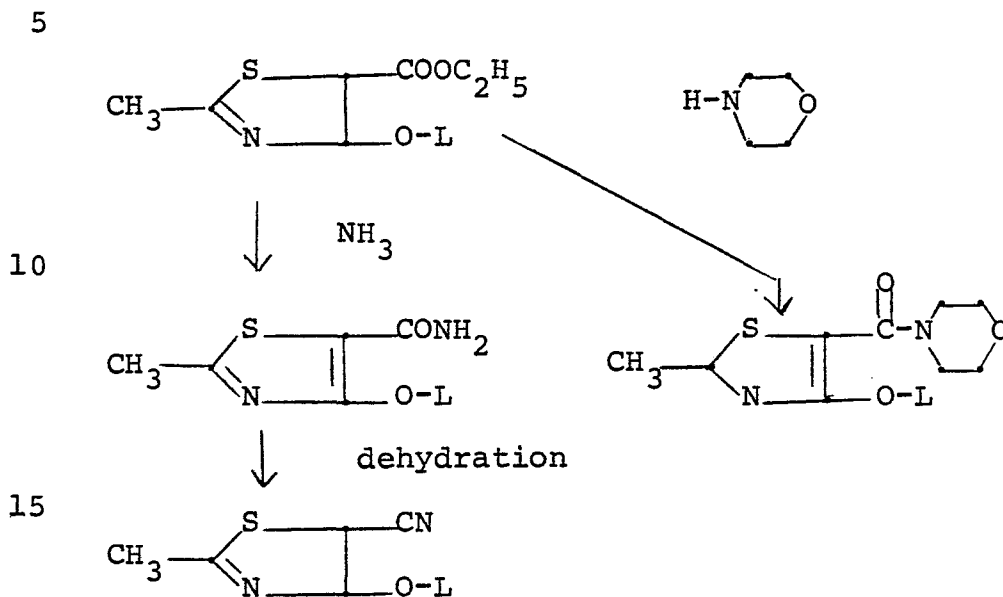


30 The compounds of the present invention also include the pharmaceutically acceptable salts of the novel thiazoles. These salts are conveniently prepared e.g. by treating the thiazole with an appropriate amount of a useful acid, generally in a
 35 suitable solvent.

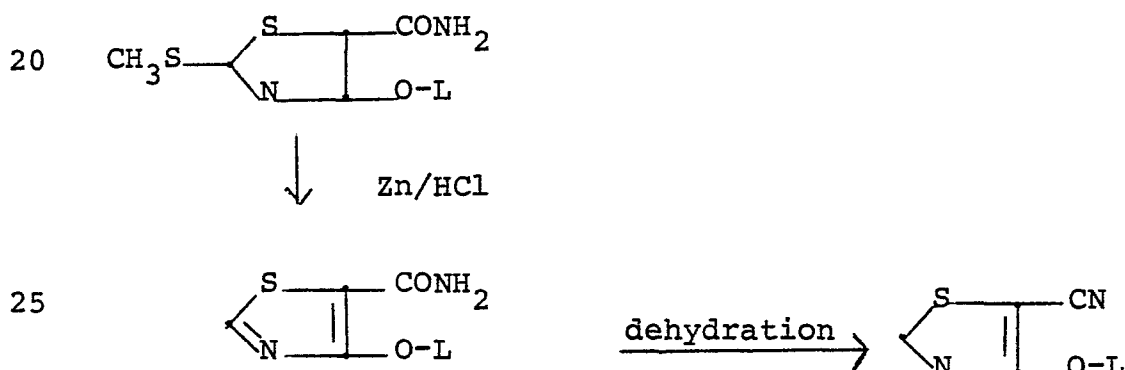
Additional processes for preparing thiazoles with certain other substituents are illustrated by

the following equation sequences. Conventional reaction conditions are employed. The symbol L represents the $-\text{CH}_2-\text{CHOR}-\text{CH}_2-\text{NR}_1$ group.

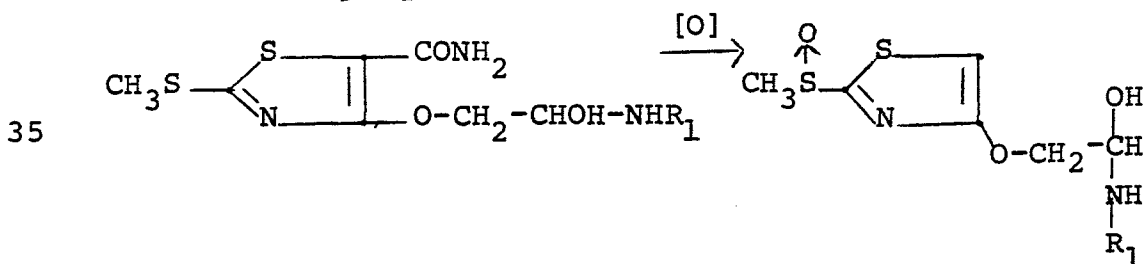
Sequence 1



Sequence 2

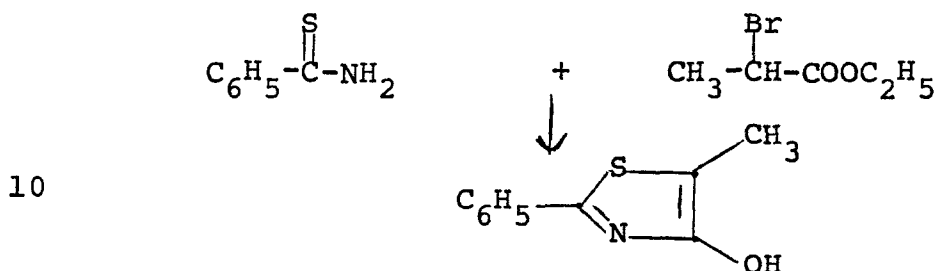


The thiazoles having an alkylsulfinyl or alkylsulfonyl substituent are prepared by oxidizing the corresponding $\text{C}_1\text{-C}_6$ alkylthio containing compound. Any suitable oxidizing agent, e.g. H_2O_2 , may be used. The following equation illustrates the reaction

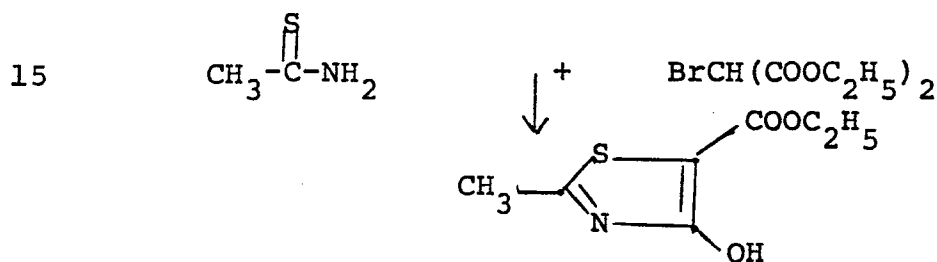


The 4-OH substituted thiazole intermediates used in the oxazolidine coupling reaction described above are prepared using conventional processes illustrated by the following equations:

5 Reaction A



Reaction B



20 The following examples illustrate preparation of representative thiazoles of the present invention. All temperatures are in °C.

EXAMPLE 1

(S) 5-Methyl-2-phenyl-4(3-tert. butylamino-2-hydroxypropoxy) thiazole hydrogen maleate salt

25 To a stirred solution of (S) 2-phenyl-3-tert.butylamino-5-hydroxymethyloxazolidine (2.5 g., 0.01m) and dry pyridine (5 ml.) is added portionwise p-toluenesulfonyl chloride (2.0 g., 0.011 m), while maintaining the temperature of the reaction below

30 30°C. After the addition, the mixture is stirred at room temperature for 3 hours. To the solid mixture is added a solution of K₂CO₃ (1.4g., 0.01 m) in H₂O (10 ml.) and the solution extracted with CHCl₃ (3 x 25 ml.). The organic layer is dried over Na₂SO₄,

35 filtered and concentrated to dryness below 50°C to yield the tosylate of (S) 2-phenyl-3-tert. butyl-

amino-2-hydroxymethyloxazolidine which is used in the next step without further purification.

Into a dry flask under N_2 is added 4-hydroxy-5-methyl-2-phenylthiazole (1.91 g., 0.1 m),
5 dimethylformamide (DMF) (20 ml.) and NaH (50% mineral oil, 0.5 g., 0.01 m). After stirring at room temperature for 15 minutes, the tosylate of (S) 2-phenyl-3-tert.-butylamino-5-hydroxymethyl-oxazolidine (0.01 m in DMF (20 ml.) is added and
10 the solution heated under reflux with stirring. After 12 hours, the solvent is removed under reduced pressure (1.5 mm). The residue is treated with 1N HCl (100 ml.) and heated on a steam bath for 3/4 hours. After cooling, the aqueous layer is extracted
15 with ether (2 x 50 ml.), neutralized with saturated Na_2CO_3 , and extracted with $CHCl_3$ (3 x 100 ml.). The organic layer is dried over Na_2SO_4 , filtered and concentrated to dryness. The residue is chromatographed on silica gel 60 and the product eluted
20 with 10% MeOH- $CHCl_3$. The crude product is crystallized with maleic acid in isopropanol (IPA)-MeOH to yield 0.25 g. (6%) of 5-methyl-2-phenyl-4(3-tert.-butylamino-2-hydroxypropoxy) thiazole hydrogen maleate salt, m.p. 174-6°C.

25 EXAMPLE 2

(S) 5-Carbamoyl-2-phenyl-4-(3-tert.-butylamino-2-hydroxypropoxy) thiazole hydrogen maleate salt.

A. Into a dry flask under N_2 is added ethyl 4-hydroxy-2-phenylthiazole-5-carboxylate (2.5 g.,
30 0.01 m), DMF (20 ml.) and NaH (50% mineral oil, 0.5 g., 0.01 m). After stirring for 15 minutes, a solution of the tosylate of (S) 2-phenyl-3-tert.-butylamino-5-hydroxymethyloxazolidine (0.01 m) in DMF (15 ml.) is added at 0-4°C. and the solution
35 heated with stirring at 100°C. After 15 hours, the solution is cooled to 0-10°C., poured into H_2O (100 ml.) and extracted with ether (3 x 100 ml.). The

- organic layer is extracted with 1N HCl (2 x 50 ml.) and the acid layer added to NaOAc (8.2 g., 0.1 m). After 5 hours, the solution is extracted with ether (2 x 50 ml.). The aqueous layer is neutralized with
- 5 saturated Na_2CO_3 and extracted with CHCl_3 (3 x 100 ml.). The organic layer is dried over Na_2SO_4 , filtered and concentrated to dryness. The residue is chromatographed on alumina (activity grade II, E. Merck) and the product eluted with 25% hexane -
- 10 CHCl_3 . The crude product is crystallized with maleic acid in CH_3CN - ether to yield 0.7 g. (14%) of (S) ethyl-2-phenyl-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole-5-carboxylate hydrogen maleate, m.p. 165-7°C.
- 15 B. A mixture of (S) ethyl-2-phenyl-4-(3-tert. butylamino-2-hydroxypropoxy)thiazole-5-carboxylate, obtained by neutralizing the product from A., (4.7 g., 0.012 m), MeOH (90 ml.) and liquid NH_3 (22 g.) is heated at 100°C. in a sealed tube.
- 20 After 24 hours, the reaction mixture is concentrated to dryness. The residue is chromatographed on alumina (activity grade II, E. Merck) and the product eluted with CHCl_3 . The crude product is crystallized with maleic acid in IPA to yield 1.65 g. (30%) of
- 25 (S) 5-carbamoyl-2-phenyl-4-(3-tert.butylamino-2-hydroxypropoxy) thiazole hydrogen maleate salt, m.p. 184-5°C.

EXAMPLE 3

- (S) 5-Cyano-2-phenyl-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole hydrogen maleate salt hemihydrate
- 30

- To triphenylphosphine oxide (2.25 g., 0.008 m) in CH_2Cl_2 (20 ml.) is added dropwise at 0-4°C. a solution of triflic anhydride (1.4 g., 0.0089 m) in CH_2Cl_2 (15 ml.). After 15 minutes, (S)
- 35 5-carbamoyl-2-phenyl-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole (1.4 g., 0.004 m) is added and the solution allowed to warm to room temperature. After

stirring overnight at room temperature, the mixture is poured into saturated Na_2CO_3 (100 ml.) and the solution extracted with CH_2Cl_2 (3 x 400 ml.). The organic layer is dried over Na_2SO_4 , filtered and concentrated to dryness. The residue is chromatographed on alumina (activity grade II, E. Merck) and the product eluted with CHCl_3 . The crude product is crystallized with maleic acid in IPA to yield 0.3 g. (16%) of (S) 5-cyano-2-phenyl-4-(3-tert.-butylamino-2-hydroxypropoxy)thiazole hydrogen maleate salt hemihydrate, m.p. 204-6°C.

EXAMPLE 4

(S) Ethyl-2-methylthio-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole-5-carboxylate hydrogen maleate salt

Into a dry flask under N_2 is added ethyl-4-hydroxy-2-methylthiazole-5-carboxylate (20 g., 0.091 m), DMF (200 ml.) and NaH (50% mineral oil, 5.0 g., 0.104 m). After stirring for 15 minutes, a solution of the tosylate of (S)-2-phenyl-3-tert.butylamino-5-hydroxymethyloxazolidine (0.106 m) in DMF (150 ml.) is added at room temperature and the solution heated on a steam bath with stirring. After 15 hours, the solution is cooled to 0-10°C., poured into H_2O (1 l.) and extracted with ether (3 x 300 ml.). The organic layer is washed with H_2O (2 x 150 ml.) and 1N HCl (3 x 233 ml.). The acid layer is added to $\text{NaOAc} \cdot 3\text{H}_2\text{O}$ (95 g., 0.7 m). After 5 hours, the solution is extracted with ether (2 x 200 ml.), neutralized with saturated Na_2CO_3 and extracted with CHCl_3 (3 x 300 ml.). The organic layer is dried over Na_2SO_4 , filtered and concentrated to dryness. The residue is chromatographed on alumina (activity grade II, E. Merck) and the product eluted with CHCl_3 . The crude product is crystallized with maleic acid in IPA- Et_2O to yield 8.8 g. (21%) of (S) ethyl 2-methylthio-4-(3-tert.butylamino-2-hydroxypropoxy)-thiazole-5-carboxylate hydrogen maleate salt, m.p.

114-116°C.

EXAMPLE 5

(S) 5-Carbamoyl-2-methylthio-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole hydrogen maleate salt

- 5 Using the same procedure described in Example 2B (S) ethyl 2-methylthio-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole-5-carboxylate (5.2 g., 0.015 m) MeOH (90 ml.) and liquid ammonia (33 g.) are heated to yield 0.9 g. (14%) of (S) 5-carbamoyl-2-methylthio-4-(3-tert.butylamino-2-hydroxypropoxy)-
10 thiazole hydrogen maleate salt, m.p. 180-2°C.

EXAMPLE 6

5 Carbamoyl-2-methyl-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole hydrogen maleate salt hemihydrate

- 15 A. Using the procedure of Example 2A, ethyl 4-hydroxy-2-methylthiazole-5-carboxylate (9.35 g., 0.05 m), DMF (100 ml.), NaH (57% mineral oil, 2.5 g., 0.052 m) and the tosylate of 2-phenyl-3-tert.butylamino-2-hydroxymethyloxazolidine (0.053 m) in DMF
20 (100 ml.) are reacted to yield 4.7 g. (30%) of ethyl 2-methyl-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole-5-carboxylate.
 B. Using the procedure of Example 2B, ethyl 2-methyl-4-(3-tert.butylamino-2-hydroxypropoxy)-
25 thiazole-5-carboxylate (4 g., 0.014 m), MeOH (90 ml.) and liquid NH₃ (33 g.) are heated to yield 1.3 g. (22%) of 5-carbamoyl-2-methyl-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole hydrogen maleate salt hemihydrate, m.p. 177-78°C.

EXAMPLE 7

5 Carbamoyl-2-methyl-4-(3-tert.butylamino-2-hydroxy-propoxy)thiazole hydrogen maleate salt hemihydrate

- A. Using the procedure of Example 2A, ethyl
5 4-hydroxy-2-methylthiazole-5-carboxylate (28 g.,
0.15 m), DMF (500 ml.), NaH (50% mineral oil, 7.5 g.,
0.16 m) and the tosylate of (S) 2-phenyl-3-tert.-
butylamino-5-hydroxymethyloxazolidine (0.15 m) in
DMF (100 ml.) are reacted to yield 9.8 g. (20%) of
10 (S) ethyl 2-methyl-4-(3-tert. butylamino-2-hydroxy-propoxy)thiazole-5-carboxylate.

- B. Using the procedure described in Example 2B,
(S) ethyl 2-methyl-4-(3-tert.butylamino-2-hydroxypropoxy)-thiazole-5-carboxylate (9.8 g., 0.034 m),
15 methanol (185 ml.) and liquid NH_3 (8.5 g.) are heated
to yield 3.6 g. (29%) of (S) 5-carbamoyl-2-methyl-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole hydrogen
maleate salt, m.p. 161-163°C.

EXAMPLE 8

- 20 (S) 5-Cyano-2-methyl-4-(3-tert.butylamino-2-hydroxy-propoxy)thiazole hydrogen maleate salt.

- Using the procedure described in Example 3,
triphenylphosphine oxide (2.78 g., 0.01 m) in
 CH_2Cl_2 (20 ml.), and (S) 5-carbamoyl-2-methyl-4-(3-
25 tert.butylamino-2-hydroxypropoxy)thiazole (1.4 g.,
0.005 m) are reacted to yield 0.9 g. (47% of (S)
5-cyano-2-methyl-4-(3-tert.butylamino-2-hydroxy-propoxy)thiazole hydrogen maleate salt, m.p. 172-
174°C.

EXAMPLE 9

5 (S) 5-Methyl-2-(4'-pyridyl)-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole.

Using the procedure in Exmample 2A, 4-hydroxy-5-methyl-2-(4'-pyridyl)thiazole (3.65 g., 0.019 m), DMF (50 ml.), NaH (57% mineral oil, 0.95 g., 0.02 m) and the tosylate of (S) 2-phenyl-3-tert.butylamino-10 5-hydroxymethyloxazolidine (0.02 m) in DMF (20 ml.) are reacted to yield 0.6 g. (10%) of (S) 5-methyl-2-(4'-pyridyl)-4-(3-tert. butylamino-2-hydroxypropoxy)-thiazole, m.p. 102-104.

EXAMPLE 10

15 (S) Ethyl 4-(3-tert.butylamino-2-hydroxypropoxy)-thiazole-5-carboxylate hydrogen maleate salt hemihydrate

To a solution of (S) ethyl 2-methylthio-4-(3-tert. butylamino-2-hydroxypropoxy)thiazole-5-carboxylate (3.6 g., 0.01 m) in 3N HCl (20 ml.) is 20 added portionwise with stirring zinc dust (2.6 g.). After 3.5 hours at room temperature, the mixture is poured into saturated Na_2CO_3 . The suspension is filtered and the filter pad washed wll with CHCl_3 . 25 The aqueous layer is extracted with CHCl_3 (3 x 75 ml.). The combined CHCl_3 extracts are dried over Na_2SO_4 , filtered and concentrated to dryness. The residue is chromatographed on silica gel and the product eluted with CHCl_3 saturated with aqueous 30 ammonia. The crude product is crystallized with maleic acid in EtOH-Et₂O to yield 0.4 g. (9%) of (S) ethyl 4-(3-tert. butylamino-2-hydroxypropoxy)-thiazole-5carboxylate hydrogen maleate salt hemihydrate, m.p. 103-105°C.

EXAMPLE 11

(S) 5-Carbamoyl-4-(3-tert.butylamino-2-hydroxypropoxy)thiazole

Using the procedure described in Example
5 10, (S) 5-carbamoyl-2-methylthio-4-(3-tert.butyl-
amino-2-hydroxypropoxy)thiazole (1.7 g., 0.005 m),
3N HCl (10 ml.) and zinc dust (0.94 g.) are reacted.
Extraction of the aqueous layer with ether yielded
unreacted starting material while extraction next
10 with CHCl₃ yielded 0.7 g. (48%) of 5-carbamoyl-4-
(3-tert. butylamino-2-hydroxypropoxy)thiazole.

EXAMPLE 12

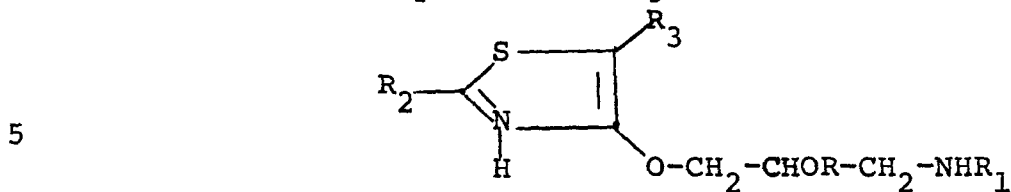
(S) 5-Cyano-4-(3-tert.butylamino-2-hydroxypropoxy)-
thiazole hydrogen maleate salt

15 Using the procedure described in Example
3, triphenylphosphine oxide (1.42 g., 0.005m) in
CH₂Cl₂ (10 ml.), triflic anhydride (0.78 ml.,
0.005 m) in CH₂Cl₂ (10 ml.) and (S) 5-carbamoyl-
4-(3-tert. butylamino-2-hydroxypropoxy)thiazole
20 (0.7 g., 0.0026 m) are reacted to yield 0.18 g. (19%)
of (S) 5-cyano-4-(3-tert.butylamino-2-hydroxypro-
poxylthiazole hydrogen maleate salt, m.p. 168-170°C.

Claims to the invention follow.

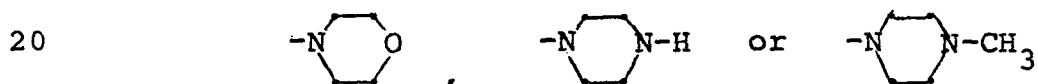
WHAT IS CLAIMED IS:

1. Compounds having the formula



and pharmaceutically acceptable salts thereof,
wherein

- R is hydrogen or C_2-C_{12} acyl,
 R_1 is C_1-C_{12} alkyl,
 10 R_2 is hydrogen, CF_3 , C_6-C_{12} carbocyclic aryl, 6-membered-N-heteroaryl, C_1-C_6 alkyl, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, thienyl and furfuryl,
 R_3 is C_1-C_6 alkyl, $-COOC_1-C_6$ alkyl, $COOC_6-C_{12}$
 15 aryl, cyano, C_6-C_{12} carbocyclic aryl, CF_3 or $-C(=O)NR_4R_5$ wherein R_4 and R_5 are independently selected from H and C_1-C_6 alkyl or are joined forming



provided that when R_2 is phenyl, R_3 is other than C_1-C_6 alkyl or $COOC_1-C_6$ alkyl.

2. Compounds of Claim 1 wherein R is
 25 hydrogen.

3. Compounds of Claim 2 wherein R_1 is C_3-C_4 branched chain alkyl.

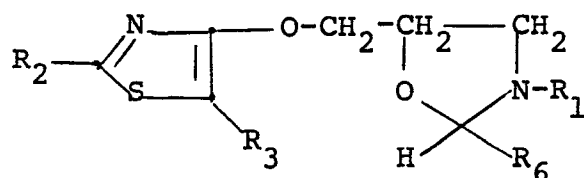
4. Compounds of Claim 3 wherein R_2 is C_1-C_6 alkyl.

30 5. Compounds of Claim 3 wherein R_2 is C_6-C_{12} carbocyclic aryl.

6. Compounds of Claim 3 wherein R_2 is C_1-C_6 alkylthio.

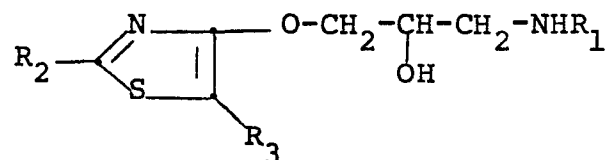
35 7. Compounds of Claim 6 wherein R_3 is $-COOC_2H_5$.

8. Compounds of Claim 3 wherein R_3 is CN,
 CNR_4R_5 or $\text{C}_1\text{-C}_6$ alkyl.
9. Compounds of Claim 8 wherein R_3 is -CN.
10. Compounds of Claim 8 wherein R_3 is
 5 -CONH₂.
11. Compounds of Claim 3 wherein R_1 is t-
 butyl, R_2 is phenyl and R_3 is $\text{-}\overset{\text{O}}{\text{C}}\text{-NH}_2$ or -CN.
12. The compounds of Claim 3 wherein R_1 is
t-butyl, R_2 is CH₃-S- and R_3 is -COOC₂H₅ or $\text{-}\overset{\text{O}}{\text{C}}\text{-NH}_2$.
13. The compounds of Claim 3 wherein R_1 is
 10 t-butyl, R_2 is -CH₃ and R_3 is $\text{-}\overset{\text{O}}{\text{C}}\text{-NH}_2$ or -CN.
14. The compounds of Claim 3 wherein R_1 is
t-butyl, R_2 is H and R_3 is -CN.
15. Compounds of Claim 1 having the S-
 isomer configuration.
16. A pharmaceutical composition for
 effecting β -adrenergic blockade containing an
 effective amount of a compound of Claim 1.
17. Compounds having the formula
- 20
-
- 25 wherein R_1 , R_2 and R_3 are defined as in Claim 1 and
 R_6 is hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl or $\text{C}_6\text{-C}_{12}$ carbocyclic
 aryl, such that when R_3 is -COOC₂H₅ R_2 must be
 -S-C₁-C₆ alkyl.
18. Compounds of Claim 17 wherein R_1 is
 30 $\text{C}_3\text{-C}_4$ branched chain alkyl and R_6 is H or phenyl.
19. Compounds of Claim 17 having the
 S-isomer configuration.
20. A process for preparing compounds of
 Claim 1 wherein R is hydrogen which comprises
 35 hydrolyzing an oxazolidine of the formula



5 wherein R_1 , R_2 and R_3 are defined as in Claim 1 and R_6 is hydrogen, C_1-C_{12} alkyl or C_6-C_{12} carbocyclic aryl.

21. A process for preparing compounds of
 Claim 1 wherein R is C_2-C_{12} acyl which comprises
 10 acylating a compound having the formula



15 wherein R_1 , R_2 and R_3 are defined as in Claim 1.



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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<u>US - A - 3 850 946 (EDWARDS)</u> * Columns 3 to 5, 11 * ---	1, 16	C 07 D 277/34 C 07 D 277/36 C 07 D 277/56 C 07 D 263/06 C 07 D 401/04 A 61 K 31/44 A 61 K 31/425 A 61 K 31/535 A 61 K 31/505
A	<u>US - A - 3 850 947 (EDWARDS)</u> * Columns 3 to 5, 10, 11 * ----	1, 16	
			TECHNICAL FIELDS SEARCHED (Int. Cl.) C 07 D 277/34 C 07 D 277/36 C 07 D 277/56 C 07 D 263/06 C 07 D 401/04 A 61 K 31/44 A 61 K 31/425 A 61 K 31/535 A 61 K 31/505
			CATEGORY OF CITED DOCUMENTS X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
The present search report has been drawn up for all claims			&: member of the same patent family, corresponding document
Place of search		Date of completion of the search	Examiner
The Hague		25-08-1978	DE BUYSER