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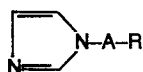
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54 **Imidazole derivatives and salts thereof, their synthesis, and intermediates, and pharmaceutical formulations.**

57 The invention relates to 1-alkylimidazoles of formula



in which A is a straight or branched, saturated or unsaturated acyclic hydrocarbon radical of from 1 to 3 carbon atoms and R is a cycloalkyl or cycloalkenyl group of from 4 to 9 carbon atoms and optionally substituted by one, two, three or more alkyl groups each containing from 1 to 4 carbon atoms, with the proviso that when A is a methylene radical, R is not unsubstituted cyclohexyl, the 1-alkylimidazole being the free base or a pharmaceutically acceptable salt thereof.

Methods of preparing these 1-alkylimidazoles are disclosed.

The 1-alkylimidazoles have pharmacological properties of use in medicine, in particular for the treatment or prophylaxis of thrombo-embolic disorders.

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Imidazole derivatives and salts thereof, their
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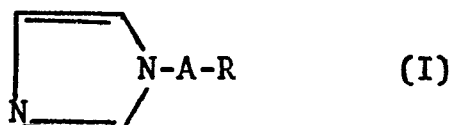
The present invention relates to imidazole
5 derivatives and salts thereof, to their synthesis
and intermediates therefor, to pharmaceutical
formulations containing such compounds and to the
use of these compounds in medicine.

Thromboxane A_2 (TXA_2), a potent stimulator
10 of blood platelet aggregation, is produced, in plate-
lets, from the prostaglandin endoperoxides PGG_2 and
 PGH_2 . Prostacyclin (PGI_2), which has potent anti-
aggregatory activity, is also produced (in blood
vessel walls) from PGG_2 and PGH_2 and it has been
15 suggested that a balance between the production of
 TXA_2 and PGI_2 is the controlling factor in thrombus
formation. It would, in consequence, be desirable
in the treatment and prophylaxis of thrombo-embolic
disorders to be able to selectively inhibit TXA_2
20 synthetase, thereby favouring the production of
the anti-aggregatory agent PGI_2 .

Imidazole and 1-methylimidazole are known to provide some degree of inhibition of the enzymic conversion of the endoperoxides (PGG₂ and PGH₂) to thromboxane A₂ by platelet
5 microsomes (Moncada et al., Prostaglandins, 13/4, 611-618, 1977). Certain 1-n-alkylimidazoles, especially 1-n-dodecylimidazole and its higher homologues have been described as being capable of lowering serum cholesterol levels (U.K. Patent
10 No. 1 364 312; Biochem. Pharmacol. 24, 1902-1903, 1975).

We have now discovered that TXA₂ synthetase may be inhibited by 1-alkylimidazoles of formula (I) and acid addition salts thereof.
15 The compounds of formula (I) and their salts are hereinafter referred to as the "active compounds".

The compounds of formula (I) are novel
and of formula:



in which A is a straight or branched, saturated
or unsaturated acyclic hydrocarbon radical of
5 from 1 to 3 carbon atoms and R is a cycloalkyl
or cycloalkenyl radical of from 4 to 9, preferably
from 5 to 8 carbon atoms and optionally substituted
by one, two, three or more alkyl radicals each
containing from 1 to 4 carbon atoms with the proviso
10 that when A is a methylene radical R is not
unsubstituted cyclohexyl.

In formula (I) examples of cycloalkyl
radicals are cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl, and cyclooctyl; cycloalkenyl radicals
15 include cyclohex-3-enyl, cyclopentenyl, 1,4-cyclo-
hexadienyl and cyclohept-2-enyl.

A valuable class of compounds of formula
(I) are those in which R is cyclohexyl, cycloheptyl,
cyclooctyl or cycloalkenyl of 6 to 8 carbon atoms
20 and A is $-\text{CH}_2-$ or $-(\text{CH}_2)_2-$. Compounds of formula (I)
may also be used as acid addition salts thereof,

especially as pharmaceutically acceptable ones.

Especially preferred compounds include:

- 1-Cyclooctylmethylimidazole
- 5 1-Cyclohex-3-enylmethylimidazole
- 1-Cyclohexylethylimidazole
- 1-Cycloheptylmethylimidazole

and acid addition salts thereof.

Other preferred compounds include:-

- 1-Cyclopentylmethylimidazole
- 1-(4-Methylcyclohexylmethyl)imidazole
- 10 1-Cyclobutylmethylimidazole
- 1-Cyclooctylvinylimidazole
- 1-(1-Cyclooctylethyl)imidazole
- 1-(2-Cyclooctylethyl)imidazole
- 1-(3-Cyclooctylpropyl)imidazole

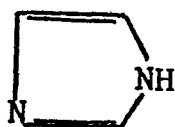
- 15 1-(Cyclohept-2-enylmethyl)imidazole
- 1-Cyclononylmethylimidazole

and acid addition salts thereof.

In contrast to imidazole and 1-methyl-imidazole the compounds of formula (I) are more potent inhibitors of TXA_2 synthetase. Many of the compounds (for example in (I) R is cycloalkyl or cycloalkenyl, n is 1, and A is $-\text{CH}_2-$ or $-(\text{CH}_2)_2-$ are also more selective in their action in not inhibiting other prostaglandin-generating enzymes such as cyclo-oxygenase. The compounds of formula (I) also do not produce the side-effects found with imidazole upon in vivo administration. The compounds of formula (I) are further capable of inhibiting platelet aggregation in vivo and also are capable of disaggregating platelet clumps. The compounds 1-cyclooctylmethylimidazole, 1-cyclohex-3-enylmethylimidazole and 1-cyclohexylethylimidazole and their salts especially displaying these properties.

Imidazoles of formula (I) and acid addition salts thereof may be made by any method known in the art for the synthesis of compounds of analogous structure. In general these methods comprise linking the imidazole ring to the remainder of the molecule; converting a precursor molecule by elimination of a functional group from the imidazole ring; and formation of the desired compound from a corresponding imidazoline, pyrazole or unsaturated analogue.

A most convenient method of synthesis involves the reaction of imidazole (formula II) or a salt thereof with an alkylating agent of formula (III):



(II)

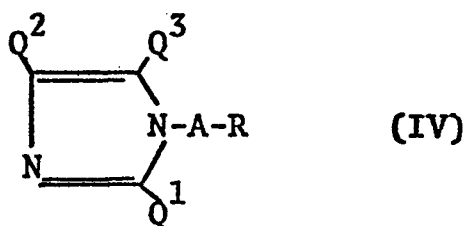


(III)

- 5 wherein R and A are as defined in formula (I) and Z is a leaving group. This reaction is well established in the literature, and the leaving group may be chosen from a variety of substituents but especially halo, preferably chloro or bromo,
- 10 or from p-toluenesulphonyloxy but other arylsulphonyloxy, alkanesulphonyloxy or aralkylsulphonyloxy radicals may be used. The reaction is preferably performed in the presence of an acid acceptor, for example an alkali metal alkoxide such as sodium
- 15 methoxide or potassium tertiary butoxide in the presence of an corresponding alkanol. The leaving group Z may itself be formed in situ from the corresponding alkanol (Z = OH) by reaction with a hydrohalogenic acid (e.g. hydrochloric acid or a
- 20 Lewis acid such as aluminium chloride: see Japanese Patent Kokai No. 131577/77) and the resulting agent

of formula (III) reacted directly with imidazole without prior isolation. Alternatively an alkanol (Z = OH) or a derivative thereof (e.g. Z = R-A-O-) may be reacted directly with imidazole (II) by
 5 heating in the presence of a dehydrating agent such as phosphoric acid, or a phosphate (see Japanese Patent Publication No. 5 1105 060), sulphuric acid or sulphates (see Japanese Patent Publication No. 5 1105 061).

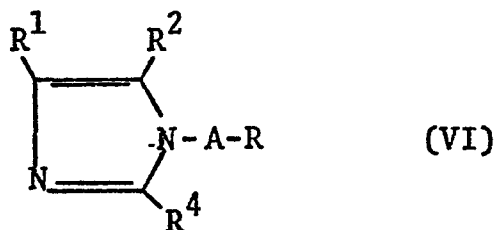
10 Among precursor molecules which may be converted to a compound of formula (I) or an acid addition salt thereof, are substituted imidazole derivatives of formula (IV) or addition salts thereof



wherein A und R are as defined in formula (I), and Q^1 , Q^2 and Q^3 are the same or different, at least one being a radical capable of removal by for example reduction or oxidation, the remaining radical or radicals being selected from hydrogen or a radical capable of removal in the same or another manner (e.g. a carboxyl group - see formula (VI) - removed by decarboxylation). Q^1 , Q^2 and Q^3 may be selected for example from thio (-SH), alkylthio (-Salkyl wherein alkyl has

1 to 4 carbon atoms) or
 halo preferably chloro or bromo. The reaction
 conditions are chosen according to the nature of
 the radicals Q^1 , Q^2 and Q^3 . Desulphurisation may
 be performed by oxidative or reductive procedures
 5 using for example nitric acid or Raney nickel;
 and reductive dehalogenation by the use of zinc
 and acetic acid or Raney nickel or other reagents
 known in the literature.

Another class of examples include carboxy-
 imidazoles or derivatives thereof of formula (VI):

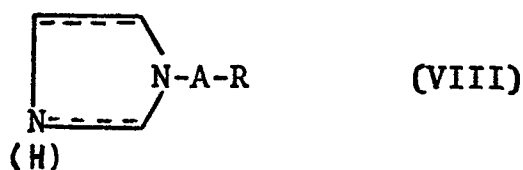


wherein A and R are as defined in formula (I),
 at least one of R^1 , R^2 and R^4 is carboxyl or a
 derivative thereof (for example an ester such as
 15 an alkyl ester, an acid halide such as the chloride,
 or the nitrile) and the other(s) is hydrogen or carboxyl
 or a derivative as described. The compounds of
 formula (VI) may be converted into the imidazoles
 of formula (I) by any suitable decarboxylation
 20 conditions which may simply comprise heating the
 compounds with or without a catalyst such as copper.

The imidazoles of formula (I) may also be made from a compound of formula (VII):



wherein (N is 1-imidazoline, 1-imidazole or 1-pyrazole, A¹ is a straight or branched saturated or unsaturated acyclic hydrocarbon radical, and R³ is a cycloalkyl or cycloalkenyl radical of from 4 to 9 carbon atoms optionally substituted by alkyl as defined in formula (I), provided that at least one of (N, A¹ and R³ is other than 1-imidazole, a saturated acyclic hydrocarbon and an optionally substituted cycloalkyl group respectively as defined in formula (I). Thus an imidazoline (VIII):

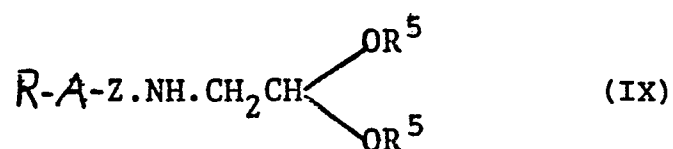


wherein one of ---- represents an extra bond, A and R are defined in formula (I) may be dehydrogenated to the corresponding imidazole in the presence of a catalyst for example by heating to 250°C in the presence of palladium, nickel or platinum under pressure, or by heating with a dehydrogenating agent such as selenium or

copper oxide. The 1-pyrazole compounds (VII) may be treated with ultra-violet irradiation, optionally under an inert atmosphere (e.g. argon) in for example 1,2-dimethoxyethane at room or
5 elevated temperatures (see for example "Ring Transformations of Heterocycles" edited van der Plas, Academic Press, 1973 at page 261). The unsaturated imidazoles of formula (I) (in formula (VII), A^1 and/or R^3 are unsaturated) may be reduced
10 to the corresponding saturated compounds with a noble metal catalyst, for example platinum or palladium in an alkanol.

The intermediates for use in the above described reactions may also be made by conventional
15 methods known in the art. Thus the 1-pyrazole and 1-imidazoline intermediates (formula (VII)) may be prepared by alkylation of pyrazole and imidazoline in an analogous manner to that described above for preparation of the corresponding imidazoles. The
20 intermediates of formula (III) may be made in known manner preferably by halogenation of the corresponding alcohols (formula (III), $Z = -OH$) where in such compounds R is cycloalkenyl, the alcohol is conveniently prepared by the Prins reaction from

the cycloalkene and paraformaldehyde (Bull. Chem. Soc. Japan 46/8, 2512-5, 1973). The substituted imidazole intermediates of formula (IV) may be made in known manner, for example see "Imidazole
5 and its derivatives" Part I, Ed. K. Hofmann, Interscience Publishers Inc. New York, 1973. For example the 2-thioimidazoles of formula (IV) may be made by cyclisation of an acetal of formula (IX):



with thiocyanate, wherein R^5 is alkyl.

10 The pharmaceutically acceptable addition salts of the compounds of formula (I) may be prepared by any method known in the art. In particular they may be prepared by treating the parent imidazole with the appropriate acid.

15 Examples of the addition salts of the compounds of formula (I) include those salts derived from the following acids: oxalic, hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic,
20 salicyclic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic,

malonic, naphthalene-2-sulphonic and benzene-sulphonic.

The imidazoles of formula (I) may be used in conjunction with a phosphodiesterase
5 inhibitor, which provides a further, synergistic increase in effect, as it acts against platelet aggregation by a different pathway.

Suitable phosphodiesterase inhibitors for use in potentiating the anti-aggregatory
10 effects of the active compounds include as such or as pharmaceutically acceptable salts:-

(a) Xanthine derivatives such as:-

Theophylline (3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione), and salts thereof.

15 3-Isobutyl-1-methyl-xanthine;

Caffeine (3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione) and salts thereof; and

Aminophylline (adduct of Theophylline and 1,2-ethanediamine (2:1)).

20 (b) Isoquinoline derivatives, for example:-

Papaverine (1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline) and salts thereof; and
6,7-Diethoxy-1-(4,5-diethoxybenzyl)isoquinoline
or its salts e.g. its hydrochloride;

(c) Derivatives of pyrimido(5,4-d)-pyrimidine, for example:-

5 Dipyridamole(2,2',2'',2'''-(4,8-dipiperidino-pyrimido [5,4-d] pyrimidin-2,6-diyl dinitrilo)-tetraethanol) and its salts;

2,2',2'',2'''-[4-(1-piperidinyl)pyrimido [5,4-d] pyrimidin-2,6-diyl] dinitrilo] tetrakisethanol and its salts; and

10 2,4,6-tri-4-morpholinylpyrimido [5,4-d] pyrimidine and its salts.

(d) Derivatives of thieno [3,2-d] pyrimidine, for example:-

N-[4-(4-morpholinyl)thieno] 3,2-d [pyrimidin-2-yl] -1,2-ethanediamine.

15 (e) Derivatives of pyrazolo [3',4':2,3] pyrido-[4,5-b] [1,5] benzodiazepin-6-(3H)-one, for example:-

3-Ethyl-7,12-dihydro-7,12-dimethylpyrazolo-[4',3':5,6] pyrido [4,3-b]- [1,5] benzodiazepin-6-(3H)-one;

20 3-Ethyl-7,12-dihydro-9-methoxy-7,12-dimethyl-pyrazolo[3',4':2,3] pyrido [4,5-b] [1,5] -benzodiazepin-6-(3H)-one; and

25 10-Chloro-3-ethyl-7,12-dimethyl-7,12-dihydro-pyrazolo [4',3':5,6] pyrido [4,3-b] [1,5] benzo-diazepin-6-(3H)-one.

(f) Derivatives of 1H- or 2H-pyrazolo[3,4-b]-pyridine, for example:-

4-(Butylamino)-1-ethyl-1H-pyrazolo[3,4-b]-pyridine-5-carboxylic acid ethyl ester;

5 4-(Butylamino)-1H-pyrazolo[3,4-b]pyridine-6-carboxylic acid ethyl ester;

4-Chloro-1-ethyl-3-methyl-1H-pyrazolo[3,4-b]-pyridine-5-acetonitrile;

10 1-Ethyl-4-(isopropylidenehydrazino)-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester or its salts such as its hydrochloride hemihydrate; and

15 2-Methyl-6-phenyl-4-(1-piperidiny1)-2H-pyrazolo[3,4-b]pyridine or its salts e.g. its hydrochloride.

(g) Derivatives of 5H-furo-[3,4-e]pyrazolo-[3,4-b]pyridine-5-one, for example:-

4-(Butylamino)-1-ethyl-1,7-dihydro-7-hydroxy-5H-furo-[3,4-e]pyrazolo[3,4-b]pyridine-5-one; and

20 (h) Derivatives of 1(2H)-naphthalenone, for example:-

2 [(Dimethylamino)methyl]-3,4-dihydro-7-methoxy-1(2H)-naphthalenone or its salts e.g. its 1:1 hydrochloride.

25 The active compounds are particularly useful in the treatment and/or prophylaxis of

thrombo-embolic disorders in mammals, including
man. It is to be understood that the term
"thrombo-embolic disorders" includes those
disorders whose etiology is associated with
5 platelet aggregation.

The active compounds are useful wherever
it is desired to inhibit platelet aggregation and/
or to reduce the adhesive character of platelets,
and consequently to treat or prevent the formation
10 of thrombi in mammals, including man. For example,
the compounds are useful in the treatment and
prevention of myocardial infarcts cerebro-vascular
thrombosis and ischaemic peripheral vascular disease;
to treat and prevent post-operative thrombosis;
15 and to promote patency of vascular grafts following
surgery.

The active compounds are also useful as
an addition to blood, blood products, blood
substitutes, and other fluids which are used in
20 artificial extra-corporeal circulation and perfusion
of isolated body portions, e.g., limbs and organs,
whether attached to the original body, detached and
being preserved or prepared for transplant, or
attached to a new body. It may also be used in

laboratory animals, e.g. cats, dogs, rabbits, monkeys and rats, for these purposes in order to develop new methods and techniques for organ and limb transplants.

5 The active compounds also exhibit some vasodilatory action on blood vessels and therefore have a utility as anti-hypertensives for the treatment of high blood pressure in mammals, including man.

10 The amount of active compound required for therapeutic or prophylactic effect will vary with the route of administration, and the nature of the condition under treatment. In general a suitable dose for a mammal, including man, of
15 active compound will lie in the range of 0.1 to 300 mg per kg body weight, particularly from 0.5 to 10 mg per kg body weight, for example 2 mg per kg. A suitable single oral dose for an adult human lies within the range of 50 to 600 mg,
20 for example 150 mg given say three times a day.

 While it is possible for the active compounds to be administered as the raw chemical it is preferable to present them as a pharmaceutical formulation. The formulations, both for veterinary
25 and for human medical use, of the present invention

comprise an active compound as above defined,
together with one or more acceptable carriers
therefor and optionally other therapeutic
ingredients. The carrier(s) must be 'acceptable'
5 in the sense of being compatible with the other
ingredients of the formulation and not deleterious
to the recipient thereof. Unit doses of a
formulation may contain between 60 mg and 1.5 g
of an active compound.

10 The formulations include those suitable
for oral, rectal, vaginal or parenteral (including
subcutaneous, intramuscular and intravenous)
administration. Preferred formulations include
tablets, capsules and injectable suspensions or
15 solutions.

 The formulations may conveniently be
presented in unit dosage form and may be prepared
by any of the methods well known in the art of
pharmacy. All methods include the step of bringing
20 into association the active compound (in the form
of the base or a pharmaceutically acceptable acid
addition salt) with the carrier which constitutes
one or more accessory ingredients. In general the
formulations are prepared by uniformly and intimately

bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired formulation.

5 It will be appreciated from the foregoing that the present invention provides the following features:-

(a) Novel 1-alkylimidazoles of formula (I), and acid addition salt thereof.

10 (b) Methods of preparing imidazoles of formula (I) and acid addition salts thereof.

(c) Pharmaceutical formulations containing the imidazoles of formula (I) or an acid addition salt thereof and a pharmaceutically acceptable
15 carrier.

(d) Method of preparing the pharmaceutical formulations containing the imidazoles of formula (I) or an acid addition salt thereof.

(e) A method for the treatment or prophylaxis
20 of a thrombo-embolic disorder in a mammal or mammalian tissue, including man or human tissue, comprising administering an active compound.

(f) An 1-alkylimidazole of formula (I)
or salt thereof as an active agent for the
treatment of a thrombo-embolic disorder in a
mammal or mammalian tissue, including man or
5 human tissue.

The following Examples are provided
by way of an illustration of the present invention
and should in no way be construed as constituting
a limitation thereof. All temperatures are given
10 in degrees Celsius.

EXAMPLE 1

1-Cyclooctylmethylimidazole

Imidazole (2.0 g, 0.03 mol) was added to a solution of sodium (0.7 g, 0.03 mol) in dry ethanol (50 ml).

- 5 The mixture was stirred and heated to boiling when bromomethylcyclooctane (5.5 g, 0.027 mol) was added dropwise. Following the addition, the reaction mixture was stirred and boiled for 15 h.

- After cooling, the reaction mixture was filtered, and
10 the filtrate concentrated under reduced pressure. The residue was dissolved in 2M-hydrochloric acid (100 ml) and the solution washed with ether (25 ml). The aqueous layer was basified with 10M-sodium hydroxide solution and then extracted with chloroform (3 x 50 ml). The chloroform extracts
15 were combined and dried (MgSO₄). Evaporation of the chloroform gave an oil which was purified using a silica gel column and elution with ethyl acetate/methanol (9:1). The product was further purified by distillation, b.p. 120-122⁰/0.2 mmHg.

EXAMPLE 2Preparation of 1-cyclopentylmethylimidazole

Imidazole (6.8 g, 0.1 mol) was added to a solution of sodium (2.3 g, 0.1 mol) in dry ethanol (100 ml). This
5 solution was stirred and heated to reflux when bromomethylcyclopentane (16.3 g, 0.1 mol) was added dropwise. Following the addition, the mixture was stirred and heated under reflux for 16 h.

After cooling, the reaction mixture was filtered and
10 the filtrate concentrated under reduced pressure. The residue was dissolved in 2M-hydrochloric acid (150 ml) and the solution washed with ether. The aqueous solution was basified with 10M-sodium hydroxide solution, and the product extracted with chloroform (3 x 50 ml). The extracts were combined,
15 dried (MgSO₄), and the solution concentrated to afford a yellow oil.

The oil was purified using a silica gel column and elution with ethyl acetate/methanol (9:1). The product fractions were combined and concentrated under reduced pressure to afford
20 1-cyclopentylmethylimidazole (1.9 g), which was further purified by distillation, b.p. 68-69⁰/0.125 mmHg.

EXAMPLE 3Preparation of 1-(3-cyclopentylpropyl)imidazole

Imidazole (1.0 g, 0.0147 mol) was added to a solution of sodium (0.34 g, 0.0148 mol) in dry ethanol (30 ml). This
5 solution was stirred and heated to boiling when 3-bromopropyl-cyclopentane (2.94 g, 0.0154 mol) was added dropwise. Following the addition, the reaction mixture was stirred and boiled for 20 h.

After cooling, the mixture was filtered and the filtrate
10 concentrated under reduced pressure. The residue was dissolved in 2M-hydrochloric acid (50 ml) and the solution washed with ether (25 ml). The acid solution was then basified with 10M-sodium hydroxide solution, and the product extracted with chloroform (3 x 25 ml). The combined extracts were dried (MgSO₄)
15 and concentrated under reduced pressure to afford a yellow oil (2.1 g).

The oil was purified by column chromatography (silica gel) using ethyl acetate/methanol (9:1) as eluent. The product fractions were combined and concentrated to afford 1-(3-cyclo-
20 pentylpropyl)imidazole which was further purified by distillation, b.p. 89-90°/0.1 mmHg.

EXAMPLE 4Preparation of 1-(cycloheptylmethyl)imidazole

Bromomethylcycloheptane (5.3 g, 0.0278 mol) was added dropwise to a stirred solution of potassium t-butoxide (3.1 g, 0.0277 mol) and imidazole (1.9 g, 0.0279 mol) in dry n-butanol (50 ml) maintained at 100° and under dry nitrogen. After the addition (~20 mins) the temperature of the reaction mixture was raised to boiling. The reaction mixture was then stirred and boiled for 7 h and then cooled.

10 The mixture was filtered, and the n-butanol was removed under reduced pressure to give a pale yellow oil. The oil was dissolved in 2M-hydrochloric acid (100 ml) and the acid solution was washed with ether (100 ml) and then basified with 10M-sodium hydroxide solution and the resulting suspension was
15 extracted with chloroform (3 x 50 ml). The chloroform extracts were combined, dried (MgSO₄), and concentrated under reduced pressure to give a pale yellow oil.

The oil was purified using a silica gel column and elution with ethyl acetate/methanol (9:1). Concentration of the
20 fractions containing 1-(cycloheptylmethyl)imidazole gave a pale yellow oil which was further purified by distillation, b.p. 92-94°/0.1 mmHg.

EXAMPLE 5Preparation of 1-(2-cyclooctenylmethyl)imidazole

(a) Preparation of 2-cyclooctene-1-methanol using the Prins reaction (Uchida *et al.*, *Bull. Chem. Soc., Japan*, 1973
5 46, 2512)

Cyclooctene (69.0 g, 0.63 mol) was added dropwise, to a stirred suspension of paraformaldehyde (24.0 g) in 98% formic acid (100 ml). After the addition, the reaction mixture was stirred and heated under reflux for 2 h. Water (100 ml) was
10 then added, and the aqueous solution was extracted with ether (50 ml). The ether solution was washed with saturated sodium bicarbonate solution (5 x 50 ml), with water (2 x 50 ml), and then dried (MgSO₄). Concentration under reduced pressure afforded a brown oil which was purified by distillation,
15 the fraction b.p. 80-110°/24 mmHg being retained.

A portion of the aforesaid oil (10 g) was treated with Claisen's alkali [potassium hydroxide (10 g), methanol (31.2 ml) and water (8 ml)], and the reaction mixture was then boiled for 2 h.

20 After cooling, the mixture was poured onto iced-water (50 ml) and extracted with ether (3 x 50 ml). The ether

extracts were combined and dried (MgSO_4). Concentration of the solution under reduced pressure afforded an oil which was distilled, to afford 2-cyclooctene-1-methanol, b.p. $128-130^\circ/23 \text{ mmHg}$.

5 (b) Preparation of 2-cyclooctene-1-bromomethane

A solution of phosphorus tribromide (1.02 ml, 0.0105 mol) in petroleum ether (b.p. $40-60^\circ$, 5 ml) was added dropwise to a stirred solution of 2-cyclooctene-1-methanol (2.8 g, 0.02 mol) and dry pyridine (0.104 g, 0.0013 mol) in petroleum ether (b.p. $40-60^\circ$; 15 ml) at -10° . After the addition, the reaction mixture was set aside at ambient temperature for 48 h.

The reaction mixture was treated with water (50 ml) and the organic layer separated. The aqueous solution was extracted with petroleum ether (b.p. $40-60^\circ$, 3 x 25 ml) and
15 the organic layer and petroleum ether extracts combined, washed with 2M-sodium hydroxide solution (25 ml), and with water (25 ml), and then dried (MgSO_4). Concentration of the solution under reduced pressure gave an oil (2.3 g) which was distilled, b.p. $48-50^\circ/0.25 \text{ mmHg}$.

(c) Preparation of 1-(2-cyclooctenylmethyl)imidazole

2-Cyclooctene-1-bromomethane (0.7 g, 0.0034 mol) was added dropwise to a boiling solution of imidazole (0.24 g, 0.0035 mol) and potassium t-butoxide (0.39 g, 0.0035 mol) 5 in dry n-butanol, under dry nitrogen. After the addition, the reaction mixture was stirred and heated under reflux for 1 h. The pure product was obtained as described in Example 4, b.p. 108-110⁰/0.02 mmHg.

EXAMPLE 6Preparation of 1-(4-methylcyclohexylmethyl)imidazole

1-Bromomethyl-4-methylcyclohexane (3.1 g, 0.0162 mol) was added dropwise to a stirred, boiling solution of imidazole
5 (1.12 g, 0.0165 mol) and potassium t-butoxide (1.85 g, 0.0165 mol) in dry n-butanol, under dry nitrogen. After the addition, the reaction mixture was stirred and heated under reflux for 10 h.

After cooling, the reaction mixture was filtered, and then
10 concentrated under reduced pressure. The residue was dissolved in 2M-hydrochloric acid (100 ml) and the solution was washed with ether (50 ml). The acid solution was basified with 10M-sodium hydroxide solution and extracted with chloroform (3 x 50 ml). The combined chloroform extracts
15 were dried (MgSO_4) and concentrated under reduced pressure. The oily residue was purified using a silica gel column and elution with ethyl acetate/methanol (9:1). The fractions containing 1-(4-methylcyclohexylmethyl)imidazole were combined, concentrated, and the resulting oil distilled, b.p. $80^\circ/0.125$ mmHg.

EXAMPLE 7

Biological Results

Horse platelets were prepared from whole horse blood by differential centrifugation.

- 5 Approximately 10^6 platelets were homogenised in 1 ml 100 mM Tris buffer pH 7.4. Various concentrations of active compound were added and the reaction sets incubated for 5 minutes at ambient temperature. To each tube was added 20 nM
- 10 of arachidonic acid containing 10^6 DPM of labelled arachidonic acid and the tubes incubated for 3 minutes at 37°C in a shaking water bath. After incubation the radioactive products were extracted from the acidified aqueous phase with ethyl acetate
- 15 and after concentration resolved by thin layer chromatography on silica gel with chloroform/methanol/acetic acid/water (90:8:1:0.8) as a developing solvent. The amount of thromboxane produced was measured by scraping the radioactive
- 20 zone corresponding to thromboxane B_2 and estimating the radioactivity in a liquid scintillation counter.

The concentration of active compound to reduce the enzyme activity by 50% (ED_{50}) was established. The results are shown in Table A.

The selectivity of the active compounds was measured in a similar manner to that described above and the amount of PGE, PGF and PGD produced was determined. The greater the selectivity, the
 5 more of the prostaglandins are produced indicating lower inhibition of cyclo-oxygenase.

The ED₅₀ and Selectivity results are shown in Table A in which 0 indicates no selectivity; + low selectivity; ++ medium selectivity; and +++ high
 10 selectivity, and ++++ exceptionally high selectivity.

TABLE A

	<u>Compound</u> <u>(Reference Compound)</u>	<u>ED₅₀</u> <u>µg/ml</u>	<u>Selectivity</u>
	(Imidazole)	≥ 500	0 to +
15	(1-Methylimidazole)	≥ 200	++
	1-Cyclopentylmethylimidazole	~ 5	+++
	1-Cyclohexylethylimidazole	4	+++
	1-Cyclooctylmethylimidazole	4	+++
	1-Cyclohex-3-enylmethylimidazole	~ 5	+++
	1-Cyclobutylmethylimidazole	50	+++
	1-Cyclopentylmethylimidazole	10.5	+++
	1-Cycloheptylmethylimidazole	4.7	++++
	1-(4-Methylcyclohexylmethyl)imidazole	6.6	+++

Example 8 - Tablet formulation

	1-Cyclooctylmethylimidazole (as a salt)	150 mg
	Starch	25 mg
	Polyvinylpyrrolidone	2 mg
5	Magnesium stearate	3 mg

The imidazole salt is ground to a fine powder, blended with the starch and then the mixture granulated with an aqueous solution of the polyvinylpyrrolidone. The granules are sieved 1000 μ , dried,
10 sieved again and the magnesium stearate added. The mixture is then compressed into tablets.

In the same manner, tablets of 1-cyclohex-3-enylmethylimidazole and 1-cyclohexylethylimidazole are prepared.

15 Example 9 - Tablet formulation

Tablets (150 mg) of the imidazoles described in the preceding example are prepared as in the same manner from the following ingredients:

	The Imidazole Compound (as a salt)	150 mg
20	Lactose	100 mg
	Starch	30 mg
	Polyvinylpyrrolidone	2 mg
	Magnesium stearate	3 mg

In the preparation, the lactose is blended
25 with the starch.

Example 10 - Tablet formulation

Tablets (100 mg) of the imidazoles of Example 8 are prepared in the same manner from the following ingredients:

- | | | |
|---|------------------------------------|--------|
| 5 | The Imidazole Compound (as a salt) | 100 mg |
| | Sodium starch glycolate | 10 mg |
| | Polyvinylpyrrolidone | 2 mg |
| | Magnesium stearate | 3 mg |

Example 11 - Tablet formulation

- 10 Tablets (150 mg) of the imidazoles of Example 8 are prepared in the same manner from the following ingredients, except that the starch, pregelled starch and imidazole compound are all blended together prior to granulation:

- | | | |
|----|------------------------------------|--------|
| 15 | The Imidazole Compound (as a salt) | 150 mg |
| | Starch | 25 mg |
| | Pregelled starch | 5 mg |
| | Magnesium stearate | 3 mg |

Example 12 - Injectable formulation

- | | | |
|----|-----------------------------------|----------------|
| 20 | Imidazole compound of formula (I) | 15.0 g |
| | Lactic Acid B.P. | q.s. to pH 3.0 |
| | Water for Injections B.P. | to 100.0 ml |

- Suspend the compound in $\frac{1}{2}$ of the available quantity of water. Add sufficient Lactic Acid to
25 dissolve the compound and to reduce the pH to 3.0.

Dilute to volume with Water for Injections.

Sterilise the solution by passage through a membrane filter, pore size 0.22 μ m.

Distribute the solution using aseptic
5 precautions into sterilised ampoules, 1 ml per ampoule. Seale by fusion of the glass.

Each 1 ml ampoule supplies 150 mg of the imidazole compound: 1-cyclooctylmethylimidazole fumarate

Example 13 - Injectable formulation

10	Imidazole compound of formula (I)	15.0 g
	Citric Acid B.P.	q.s. to pH 3.0
	Chlorocresol	0.1 g
	Water for Injections to	100.0 ml

Suspend the compound in $\frac{1}{2}$ the final volume
15 of Water for Injections. Add sufficient Citric Acid as a 10% solution in Water for Injections to dissolve the compound and reduce the pH to 3.0. Dilute to volume with Water for Injections.

Sterilise the solution by passage through a
20 membrane filter, pore size 0.22 μ m.

Distribute the solution with aseptic precautions into sterilised vials, 25 ml per vial. Stopper with sterile rubber closures and seal with an aluminium cap.

Each 1 ml of solution provides 150 mg
of the compound: 1-cyclooctylmethylimidazole fumarate.

Example 14 - Injectable formulation

In the manner described in the preceding
5 two Examples, injectable formulations of 1-
cyclohexylethylimidazole and 1-cyclohex-3-
enylmethylimidazole salts were prepared.

EXAMPLE 15

By the method described in Example 1 above
10 the following compounds were prepared:-

- (a) 1-(cyclooctylvinyl)imidazole
- (b) 1-(2-cyclooctylethyl)imidazole
- (c) 1-(cyclooctylethyl)imidazole
- (d) 1-(3-cyclooctylpropyl)imidazole
- 15 (e) 1-(3-methylcyclohept-2-enylmethyl)imidazole
- (f) 1-(3-methylcycloheptylmethyl)imidazole
- (g) 1-(cyclohex-3-enylmethyl)imidazole m.p. 36-37°C
- (h) 1-(cyclohexylethyl)imidazole b.p. 95-96/0.2 mm
- (i) 1-(cyclobutylmethyl)imidazole b.p. 148-150/25 mm.
- (j) 1-(cyclononylmethyl)imidazole

Example 16 - Salts of 1-CyclooctylmethylimidazoleA. Hydrogen Fumarate

A solution of fumaric acid (0.22 g) in hot ethanol (10 ml) was added to a solution of 1-cyclooctylmethylimidazole (0.38 g) in ethanol (4 ml). After boiling for 10 minutes the solution was evaporated to afford a white solid. Recrystallisation from ethyl acetate afforded 1-cyclooctylmethylimidazole hydrogen fumarate (0.42 g) as white needles, m.p. 147-148°.

B. Hydrogen Succinate

A solution of succinic acid (0.23 g) in ethanol (~ 5 ml) was added to a solution of 1-cyclooctylmethylimidazole (0.38 g) in ethanol (5 ml). Evaporation of the solution afforded a white solid. Recrystallisation of the solid from ethyl acetate afforded 1-cyclooctylmethylimidazole ^{hydrogen succinate} (0.27 g) as colourless plates, m.p. 86-87°.

C. Oxalate

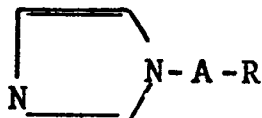
A solution of oxalic acid (0.17 g) and 1-cyclooctylmethylimidazole (0.38 g) in ethanol (20 ml) was boiled for 0.25 h, when evaporation of the solution afforded a white solid. Recrystallisation of the solid from ethyl acetate/ethanol/petroleum ether (b.p. 40-60°) afforded 1-cyclooctylmethylimidazole oxalate as white needles, m.p. 141-142°.

D. Hydrochloride

1-Cyclooctylmethylimidazole (~ 0.3 g) was dissolved in dry ether (30 ml), when a stream of dry hydrogen chloride was passed through the solution at -20°. The resulting white precipitate was filtered off under dry nitrogen and recrystallised from ethyl acetate/petroleum ether (b.p. 40-60°) to afford 1-cyclooctylmethylimidazole hydrochloride as a white solid, m.p. 20-22°C.

What we claim is:-

1. A 1-alkylimidazole characterised in that said compound has the formula



in which A is a straight or branched, saturated
5 or unsaturated acyclic hydrocarbon radical of
from 1 to 3 carbon atoms and R is a cycloalkyl or
cycloalkenyl group of from 4 to 9 carbon atoms and
optionally substituted by one, two, three or more
alkyl groups each containing from 1 to 4 carbon
10 atoms, with the proviso that when A is a methylene
radical, R is not unsubstituted cyclohexyl, the
alkylimidazole being the free base or a pharmaceu-
tically acceptable salt thereof.

2. A 1-alkylimidazole as defined in claim 1
15 characterised in that A is $-\text{CH}_2-$ or $-(\text{CH}_2)_2-$, and
R is cycloalkyl or cycloalkenyl as defined.

3. A 1-alkylimidazole as defined in claim 2
characterised in that R is cyclopentyl, cyclohexyl,
cyclooctyl or cyclohexenyl.

4. A 1-alkylimidazole characterised in that
it is selected from 1-cyclohex-3-enylmethylimidazole,
1-cyclohexylethylimidazole, 1-cyclopentylmethylimidazole
1-cycloheptylmethylimidazole, 1-cyclobutylmethylimidazole
5 and acid addition salts thereof.

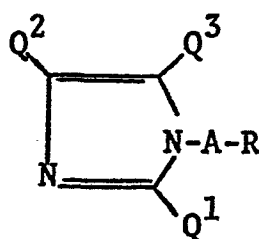
5. 1-Cyclooctylmethylimidazole or an acid
addition salt thereof.

6. 1-Cyclooctylmethylimidazole.

7. A method of preparing a 1-alkylimidazole
10 or an acid addition salt thereof as defined in
claim 1 characterised in that one reacts imidazole
or a salt thereof with an alkylating agent of the
formula $Z-A-R$ wherein A and R are as defined in
claim 1 and Z is a leaving group.

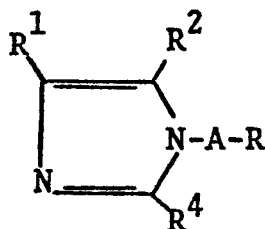
15 8. A method of preparing a 1-alkylimidazole
of the formula defined in any of claims 1 to 6
or an acid addition salt thereof characterised
in that one

(a) converts a substituted imidazole of the
formula



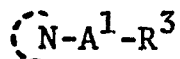
wherein A and R are defined in formula (I) and Q^1
 Q^2 and Q^3 are the same or different, at least
 one being a radical capable of removal, the other
 being a radical having the same function or is
 5 hydrogen;

(b) decarboxylates a mono- or dicarboxyimidazole
 derivative of the formula



wherein A and R are defined in formula (I), at
 least one of R^1 , R^2 and R^4 is carboxyl or a
 10 derivative thereof, and the others are hydrogen,
 carboxyl or a derivative thereof;

(c) converts a precursor of the formula



wherein $\bar{N}$ is 1-imidazoline, 1-imidazole or 1-pyrazole,
 A^1 is a straight or branched saturated or unsaturated
 15 acyclic hydrocarbon radical, and R^3 is a cycloalkyl
 or cycloalkenyl radical of 4 to 9 carbon atoms
 optionally substituted by alkyl as defined in formula
 (I) provided that at least one of $\bar{N}$, A^1 and R^3 is

0000950

- 4 -

A549 A

other than 1-imidazole, a saturated acyclic hydrocarbon and an optionally substituted cycloalkyl group as defined in formula (I) respectively.



DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ²)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	<u>DE - A - 2 533 211 (HEUMANN)</u> * Pages 12 and 13 * -----	1-6	C 07 D 233/58 A 61 K 31/415
			TECHNICAL FIELDS SEARCHED (Int.Cl. ²)
			C 07 D 233/58
			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
			&: member of the same patent family, corresponding document
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 27-11-1978	Examiner DE BUYSER I.