

PATENT SPECIFICATION

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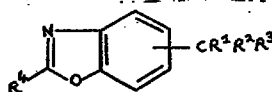
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 and TERENCE ALAN HICKS

(54) BENZOXAZOLE DERIVATIVES

(71) We, LILLY INDUSTRIES LIMITED, a British company of Henrietta House, Henrietta Place, London, W.1., 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 certain new benzoxazole derivatives which have been found to possess valuable pharmacological activity or are useful as intermediates for preparing such active compounds and to a process by which such compounds may be prepared. The invention also includes pharmaceutical compositions containing said pharmacologically active compounds.

According to the present invention therefore, there is provided a novel benzoxazole derivative of the formula:



I

wherein the group $-CR^1R^2R^3$ is in the 5- or 6-position of the benzoxazole nucleus, R^1 and R^2 are independently hydrogen or C_{1-6} alkyl, R^3 is a nitrile group, carboxy or a salt, ester, amide or hydroxamic acid derivative thereof, or hydroxymethyl or an ester derivative thereof, and R^4 is cyclohexyl, or a heteroaryl or phenyl group optionally substituted in any available position by one or more radicals selected from C_{1-6} alkylsulphonyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, nitro, C_{2-7} acyl, hydroxy, amino, C_{1-6} alkylamino and C_{2-7} acylamino, or optionally substituted in two adjacent positions by methylene or ethylene-dioxy; provided that R^4 cannot be a 3-alkyl-4-hydroxyphenyl or a 3,5-dialkyl-4-hydroxyphenyl group.

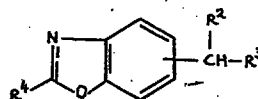
The term " C_{1-6} alkyl" as used herein means a straight or branched chain alkyl group containing from 1 to 6 carbon atoms such as methyl, ethyl, isopropyl, *n*-butyl, *s*-butyl, *t*-butyl, *n*-amyl, *s*-amyl, *n*-hexyl, 2-ethylbutyl and 4-methylamyl. The terms " C_{1-6} alkoxy", " C_{1-6} alkylsulphonyl", " C_{1-6} alkylamino", " C_{2-7} acyl", and " C_{2-7} acylamino" mean the aforementioned C_{1-6} alkyl groups linking through an oxygen atom, or an $-SO_2-$, $-NH-$, $-CO-$ or $-CONH-$ group respectively. The term " C_{1-6} haloalkyl" as used herein means the aforementioned C_{1-6} alkyl groups substituted by one or more halogen atoms such as, for example, chloromethyl, bromomethyl, trifluoro-

methyl, 2-chloroethyl, pentafluoroethyl, 3-bromopropyl, 2-chlorobutyl, 4-bromobutyl, 2-(2-chloroethyl)-3-chloropropyl and 6-chlorohexyl. The term "heteroaryl" as used herein means a heterocyclic aromatic group containing at least one ring atom which is not carbon, preferred examples of which are 5- or 6-membered heterocyclic aromatic rings containing one or two ring atoms selected from oxygen, sulphur and nitrogen.

Within the aforementioned group of compounds of formula I, there is a sub-group preferred for the ease of availability of the necessary starting materials, which sub-group comprises compounds wherein the group $-\text{CR}^1\text{R}^2\text{R}^3$ is in the 5- or 6-position of the benzoxazole nucleus, R^4 is cyclohexyl, furyl, thienyl, pyridyl, pyrazinyl, or a phenyl group optionally substituted in any available position by one or two radicals selected from halogen, nitro, amino, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, pentafluoroethyl and C_{1-4} -monohaloalkyl or optionally substituted in two adjacent positions by methylene- or ethylene-dioxy, R^1 and R^2 are independently hydrogen, methyl or ethyl, and R^3 is:

- (i) the group $-\text{COOR}^5$, where R^5 is C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl or di- C_{1-4} alkylamino- C_{1-4} alkyl; or
- (ii) the group $-\text{CO}-\text{R}^6$ where R^6 is $-\text{NHOH}$ or $-\text{NR}^7\text{R}^8$ where R^7 and R^8 are independently hydrogen or C_{1-4} alkyl; or
- (iii) the group $-\text{CH}_2\text{OR}^9$ where R^9 is hydrogen or C_{1-4} alkyl; or
- (iv) the group $-\text{COOH}$ or an alkali or alkaline earth metal, aluminium or ammonium salt thereof; or
- (v) a nitrile group.

Using standard test procedures in animals, compounds of the foregoing type have been assessed for pharmacological activity and lack of toxicity. Such tests have revealed a further group of compounds in which the combination of high activity, especially anti-inflammatory activity, and low toxicity is most marked. This especially useful group of compounds falls within the general formula:



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wherein the group



is in the 5- or 6-position of the benzoxazole nucleus, R^4 is a phenyl group optionally substituted by one or two radicals selected from halogen, trifluoromethyl, methyl, methoxy and nitro, R^2 is hydrogen or most advantageously methyl, and R^3 is as defined in parts (i) to (iv) above, especially $-\text{COOR}^5$ where R^5 is C_{1-4} alkyl or the group $-\text{COOH}$ or an alkali or alkaline earth metal, aluminium or ammonium salt thereof.

Examples which may be given of the compounds of this invention are:

2-cyclohexyl-5-benzoxazolyl-acetic acid
 2-cyclohexyl-5-benzoxazolyl-acetonitrile
 2-cyclohexyl-6-benzoxazolyl-acetic acid
 methyl 2-(2-cyclohexyl-5-benzoxazolyl) propionate
 2-dimethylaminoethyl 2-cyclohexyl-5-benzoxazolyl-acetate
 potassium 2-(2-cyclohexyl-5-benzoxazolyl) butyrate
 2-[2-(fur-2-yl)-5-benzoxazolyl]-2-methylpropionic acid
 2-[2-(fur-2-yl)-6-benzoxazolyl] propionic acid
t-butyl 2-(fur-2-yl)-5-benzoxazolyl acetate
 2-[2-(fur-3-yl)-5-benzoxazolyl] ethanol
 2-[2-(fur-2-yl)-5-benzoxazolyl] propionitrile
 2-[2-(thien-2-yl)-5-benzoxazolyl] propyl alcohol
 2-[2-(thien-2-yl)-6-benzoxazolyl]-2-ethyl-propionic acid
 ethyl 2-(thien-3-yl)-5-benzoxazolyl-acetate
 2-(thien-3-yl)-5-benzoxazolyl-acethydroxamic acid
 2-(pyrid-4-yl)-5-benzoxazolyl-acetic acid
 2-(pyrid-2-yl)-6-benzoxazolyl-acetonitrile
 2-[2-(pyrid-2-yl)-5-benzoxazolyl] propionic acid
 isopropyl 2-[2-(pyrid-2-yl)-6-benzoxazolyl] propionate
 2-[2-(pyrid-2-yl)-6-benzoxazolyl] propyl alcohol

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	2	3	1,435,721	3
yl, ed is tic			2-(pyrazin-2-yl)-6-benzoxazolyl-acetic acid	
			2-(pyrazin-2-yl)-6-benzoxazolyl-ethyl alcohol	
			2-[2-(pyrazin-2-yl)-5-benzoxazolyl] propionic acid	
			ethyl 2-[2-(pyrazin-2-yl)-5-benzoxazolyl] propionate	
up ib- of		5	2-[2-(4-chlorophenyl)-5- and 6-benzoxazolyl] propionitrile	5
yl ed	10	10	2-(4-nitrophenyl)-5-benzoxazolyl-acetic acid	
yl- yl- nd			2-(4-aminophenyl)-6-benzoxazolyl-acetic acid	
			ethyl 2-[2-(3,4-methylenedioxyphenyl)-5-benzoxazolyl] propionate	
			2-[2-(4-β-chloroethylphenyl)-6-benzoxazolyl] propionic acid	
			2-[2-(3,4-diethylphenyl)-5-benzoxazolyl] propionic acid	10
			2-(3-ethoxyphenyl)-5-benzoxazolyl-acethydroxamic acid	
			2-[2-(4-hydroxyphenyl)-6-benzoxazolyl] ethanol	
yl-	15	15	ethyl 2-(4-dimethylaminophenyl)-5-benzoxazolyl-acetate	
R ^o			2-(3,4-dihydroxyphenyl)-5-benzoxazolylacetic acid	
			2-[2-(4- <i>t</i> -butoxyphenyl)-6-benzoxazolyl] butyric acid	15
or	20	20	2-[2-(4-chlorophenyl)-5-benzoxazolyl] butyronitrile	
			2-diethylaminoethyl 2-(2-methoxyphenyl)-5-benzoxazolyl-acetate	
			2-[2-(2,4-dinitrophenyl)-5-benzoxazolyl] propyl alcohol	
			2-[2-(4-aminophenyl)-6-benzoxazolyl] propionylhydroxamic acid	
			sodium 2-(4- <i>n</i> -butylphenyl)-5-benzoxazolyl acetate.	20
en f a nti- of	25		Examples of preferred compounds of the present invention are:	
		A	(i) 2-phenyl-5- and 6-benzoxazolyl-acetic acid	
			2-(4-chlorophenyl)-5- and 6-benzoxazolyl-acetic acid	
		25	2-(4-methylphenyl)-5- and 6-benzoxazolyl-acetic acid	
			2-(4-trifluoromethylphenyl)-5- and 6-benzoxazolyl-acetic acid	25
			2-(4-methoxyphenyl)-5- and 6-benzoxazolyl-acetic acid	
			2-(4-bromophenyl)-5- and 6-benzoxazolyl-acetic acid	
			2-(4-fluorophenyl)-5- and 6-benzoxazolyl-acetic acid	
		30	2-(3-chlorophenyl)-5- and 6-benzoxazolyl-acetic acid	
			2-(3-methylphenyl)-5- and 6-benzoxazolyl-acetic acid	30
			2-(3-trifluoromethylphenyl)-5- and 6-benzoxazolyl-acetic acid	
			2-(3,4-dichlorophenyl)-5- and 6-benzoxazolyl-acetic acid	
			2-(2-methylphenyl)-5- and 6-benzoxazolyl-acetic acid	
		35	2-(2-chlorophenyl)-5- and 6-benzoxazolyl-acetic acid	
	30		2-(2-methoxyphenyl)-5- and 6-benzoxazolyl-acetic acid	35
			2-(3,4-dimethylphenyl)-5- and 6-benzoxazolyl-acetic acid	
ally hyl, ned oup f.	35	A	(ii) the sodium, potassium, aluminium and ammonium salts of the acids of A(i) above,	
		A	(iii) the C ₁₋₄ alkyl, amino-C ₁₋₄ alkyl, dimethylamino-C ₁₋₄ alkyl and diethylamino-C ₁₋₄ alkyl esters of the acids of A(i) above,	40
		B.	2-phenyl-5- and 6-benzoxazolyl-acetamide	
			2-phenyl-5- and 6-benzoxazolyl-acethydroxamic acid	
			2-(4-chlorophenyl)-5- and 6-benzoxazolyl-acethydroxamic acid	
		45	2-(4-chlorophenyl)-5- and 6-benzoxazolyl-acetamide	
			2-(4-bromophenyl)-5- and 6-benzoxazolyl-acetamide	45
			2-(4-fluorophenyl)-5- and 6-benzoxazolyl-acetamide	
	40		2-(4-methylphenyl)-5- and 6-benzoxazolyl-acetamide	
			2-(4-methoxyphenyl)-5- and 6-benzoxazolyl-acetamide	
		50	2-(2-methoxyphenyl)-5- and 6-benzoxazolyl-acetamide	
			2-(2-chlorophenyl)-5- and 6-benzoxazolyl-acetamide	50
			2-(3,4-dichlorophenyl)-5- and 6-benzoxazolyl-acetamide	
	45		2-(3-chlorophenyl)-5- and 6-benzoxazolyl-acetamide	
			2-(3-methylphenyl)-5- and 6-benzoxazolyl-acetamide	
		55	2-(4-trifluoromethylphenyl)-5- and 6-benzoxazolyl-acetamide	
			2-(4-trifluoromethylphenyl)-5- and 6-benzoxazolyl-acethydroxamic acid	55
			2-(4-bromophenyl)-5- and 6-benzoxazolyl-acethydroxamic acid	
	50		2-(4-fluorophenyl)-5- and 6-benzoxazolyl-acethydroxamic acid	
			2-(3,4-dimethylphenyl)-5- and 6-benzoxazolyl-acethydroxamic acid	
		60	2-(4-methoxyphenyl)-5- and 6-benzoxazolyl-acethydroxamic acid	
			2-(4-methylphenyl)-5- and 6-benzoxazolyl-acethydroxamic acid	60
			2-(3-chlorophenyl)-5- and 6-benzoxazolyl-acethydroxamic acid	
	55		2-[2-(3-chlorophenyl)-5- and 6-benzoxazolyl]propionylhydroxamic acid	
			2-[2-(4-chlorophenyl)-5- and 6-benzoxazolyl]propionylhydroxamic acid	

- 2-[2-(2-chlorophenyl)-5- and 6-benzoxazolyl]propionylhydroxamic acid
 2-[2-(3,4-dichlorophenyl)-5- and 6-benzoxazolyl]propionylhydroxamic acid
 2-[2-(4-trifluoromethylphenyl)-5- and 6-benzoxazolyl]propionylhydroxamic acid
 5 2-[2-(4-methylphenyl)-5- and 6-benzoxazolyl]propionylhydroxamic acid 5
 2-[2-(4-methoxyphenyl)-5- and 6-benzoxazolyl]propionylhydroxamic acid
 2-[2-(3-methoxyphenyl)-5- and 6-benzoxazolyl]propionamide
 2-[2-(4-methylphenyl)-5- and 6-benzoxazolyl]propionamide
 10 2-[2-(4-trifluoromethylphenyl)-5- and 6-benzoxazolyl]propionamide 10
 2-[2-(4-methoxyphenyl)-5- and 6-benzoxazolyl]propionamide
 2-[2-(4-chlorophenyl)-5- and 6-benzoxazolyl]propionamide
 2-[2-(4-bromophenyl)-5- and 6-benzoxazolyl]propionamide
 2-[2-(4-fluorophenyl)-5- and 6-benzoxazolyl]propionamide

- C (i) 2-[2-phenyl-5- and 6-benzoxazolyl]ethanol 15
 2-[2-(4-chlorophenyl)-5- and 6-benzoxazolyl]ethanol 15
 2-[2-(4-methylphenyl)-5- and 6-benzoxazolyl]ethanol
 2-[2-(4-trifluoromethylphenyl)-5- and 6-benzoxazolyl]ethanol
 2-[2-(4-methoxyphenyl)-5- and 6-benzoxazolyl]ethanol
 20 2-[2-(4-bromophenyl)-5- and 6-benzoxazolyl]ethanol 20
 2-[2-(4-fluorophenyl)-5- and 6-benzoxazolyl]ethanol
 2-[2-(3-chlorophenyl)-5- and 6-benzoxazolyl]ethanol
 2-[2-(3-methylphenyl)-5- and 6-benzoxazolyl]ethanol
 25 2-[2-(2-methylphenyl)-5- and 6-benzoxazolyl]ethanol 25
 2-[2-(2-methoxyphenyl)-5- and 6-benzoxazolyl]ethanol
 2-[2-(2-chlorophenyl)-5- and 6-benzoxazolyl]ethanol
 2-[2-(2-chlorophenyl)-5- and 6-benzoxazolyl]propyl alcohol
 2-[2-(3-chlorophenyl)-5- and 6-benzoxazolyl]propyl alcohol
 30 2-[2-(4-chlorophenyl)-5- and 6-benzoxazolyl]propyl alcohol 30
 2-[2-(3,4-dichlorophenyl)-5- and 6-benzoxazolyl]propyl alcohol
 2-[2-(3,4-dimethylphenyl)-5- and 6-benzoxazolyl]propyl alcohol
 2-[2-(3-methylphenyl)-5- and 6-benzoxazolyl]propyl alcohol
 2-[2-(4-methylphenyl)-5- and 6-benzoxazolyl]propyl alcohol
 35 2-[2-(4-trifluoromethylphenyl)-5- and 6-benzoxazolyl]propyl alcohol 35
 2-[2-(4-methoxyphenyl)-5- and 6-benzoxazolyl]propyl alcohol
 2-[2-(4-bromophenyl)-5- and 6-benzoxazolyl]propyl alcohol
 2-[2-(4-fluorophenyl)-5- and 6-benzoxazolyl]propyl alcohol
 2-[2-(2-methylphenyl)-5- and 6-benzoxazolyl]propyl alcohol
 2-[2-(2-methoxyphenyl)-5- and 6-benzoxazolyl]propyl alcohol

- 40 C (ii) the C₁₋₄ alkyl esters of the alcohols of C(i) above. 40

Examples of the most preferred compounds of the invention are:

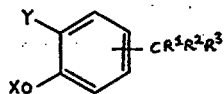
- D (i) 2-[2-phenyl-5- and 6-benzoxazolyl]propionic acid
 2-[2-(3,4-dimethoxyphenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(3,4-methylenedioxyphenyl)-5- and 6-benzoxazolyl]propionic acid
 45 2-[2-(2-chlorophenyl)-5- and 6-benzoxazolyl]propionic acid 45
 2-[2-(2-fluorophenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(2-methylphenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(3,4-dichlorophenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(3,5-dichlorophenyl)-5- and 6-benzoxazolyl]propionic acid
 50 2-[2-(2,4-dichlorophenyl)-5- and 6-benzoxazolyl]propionic acid 50
 2-[2-(3-chlorophenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(3-trifluoromethylphenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(3-fluorophenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(3-methylphenyl)-5- and 6-benzoxazolyl]propionic acid
 55 2-[2-(4-iodophenyl)-5- and 6-benzoxazolyl]propionic acid 55
 2-[2-(4-chlorophenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(2-hydroxy-4-chlorophenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(4-bromophenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(4-nitrophenyl)-5- and 6-benzoxazolyl]propionic acid
 60 2-[2-(4-fluorophenyl)-5- and 6-benzoxazolyl]propionic acid 60
 2-[2-(3-nitro-4-chlorophenyl)-5- and 6-benzoxazolyl]propionic acid

- 2-[2-(4-methylphenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(2-acetylphenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(4-trifluoromethylphenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(4-methoxyphenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(4-methylsulphonylphenyl)-5- and 6-benzoxazolyl]propionic acid
 2-[2-(2-methoxyphenyl)-5- and 6-benzoxazolyl]propionic acid

D (ii) the sodium, potassium, aluminium and ammonium salts of the acids of D(i) above, and

D (iii) the C_{1-4} alkyl, amino- C_{1-4} alkyl, dimethylamino- C_{1-4} alkyl and diethylamino- C_{1-4} alkyl esters of the acids of D(i) above.

The present invention also provides a process for preparing the foregoing compounds of formula I which comprises cyclising a compound of the formula:



III

wherein either X is hydrogen or the group R^4CO- and Y is H_2N- or X is hydrogen and Y is the group $R^4CO-NH-$ or $R^4CH=N-$, the cyclisation being carried out, in the case where X is hydrogen and Y is H_2N- , in the presence of a cyclising agent capable of donating the required group R^4 . The compounds of formula III are described and claimed in the specification of co-pending application No. 47016/75 (Serial No. 1435722).

In carrying out the foregoing cyclisation using a compound of formula III in which X is hydrogen and Y is H_2N- , it will be appreciated that, if R^3 is also capable of reacting with the cyclising agent used, the reaction may produce a mixture of products rather than the desired compound of formula I alone. The desired products can be recovered from the reaction mixture, although it is obviously desirable to use a compound of formula III in which R^3 is a group which is incapable of reaction with the cyclising agent. For instance, if it is desired to prepare a compound of formula I in which R^3 is carboxy, this compound may conveniently be prepared by cyclisation of a compound of formula III in which R^3 is nitrile, followed by hydrolysis of the product.

The cyclisation of a compound of formula III in which X is hydrogen and Y is $R^4CO-NH-$ or in which X is R^4CO- and Y is H_2N- may be carried out under the influence of heat and/or under acidic conditions, for example in the presence of hydrochloric acid or polyphosphoric acid. In the case where X is hydrogen and Y is $R^4CH=N-$, cyclisation is easily accomplished by treatment with an oxidising agent such as lead tetra-acetate or nickel peroxide.

When a compound of formula III in which X is hydrogen and Y is H_2N- is used, cyclisation is normally accomplished by mixing the cyclising agent with the compound of formula III, usually in a suitable solvent which may be water or an organic solvent, such as pyridine, at room temperature or below, followed by the application of heat to complete the reaction. Examples of suitable cyclising agents which may be used are compounds of the formulae R^4COOH , $(R^4CO)_2O$, R^4COCl , R^4CONH_2 , $R^4CONHNH_2$, R^4CN , $R^4C(OR')=NH$ and $R^4CCl=NR'$ where R' is C_{1-6} alkyl.

Nitriles of formula I may be prepared by cyclising a compound of formula III where R^3 is hydrogen and then halogenating the product of the cyclisation reaction using, for example, chlorine, sulphuryl chloride, bromine or N-bromosuccinimide, preferably in the presence of a suitable solvent such as carbon tetrachloride to produce the corresponding compound in which R^3 is halogen. This compound, or the same compound obtained directly from the above cyclisation reaction, may then be reacted with an alkali metal cyanide in a suitable diluent or solvent, usually under the influence of heat, to produce the nitrile of formula I.

The latter compound, or the same compound obtained directly from the above cyclisation reaction, may then be treated in a number of ways to achieve its conversion to another compound of formula I. For example, as mentioned previously the nitrile may be reacted with an appropriate alcohol under acidic conditions to produce a compound of formula I in which R^3 is an esterified carboxy group. Alternatively, the nitrile can be hydrolysed, for example using sulphuric acid, to produce a compound of formula I in which R^3 is a carboxyl group. Hydrolysis of the nitrile, or the last mentioned amide, with a strong base or an acid such as concentrated hydrochloric

acid, results in the formation of a compound of formula I in which R^3 is a carboxy group. A resultant compound of formula I in which R^3 is esterified carboxy may be converted to a hydroxamic acid derivative by reaction with hydroxylamine. A resultant acid of formula I, i.e. where R^3 is a carboxy group, or an ester thereof may readily be reduced, for example using diborane or a complex metal hydride, to yield the corresponding compound of formula I in which R^3 is hydroxymethyl and the alcohol resulting therefrom may then be esterified in conventional manner, for example by reaction with an appropriate carboxylic acid such as a C_{2-4} alkanolic acid.

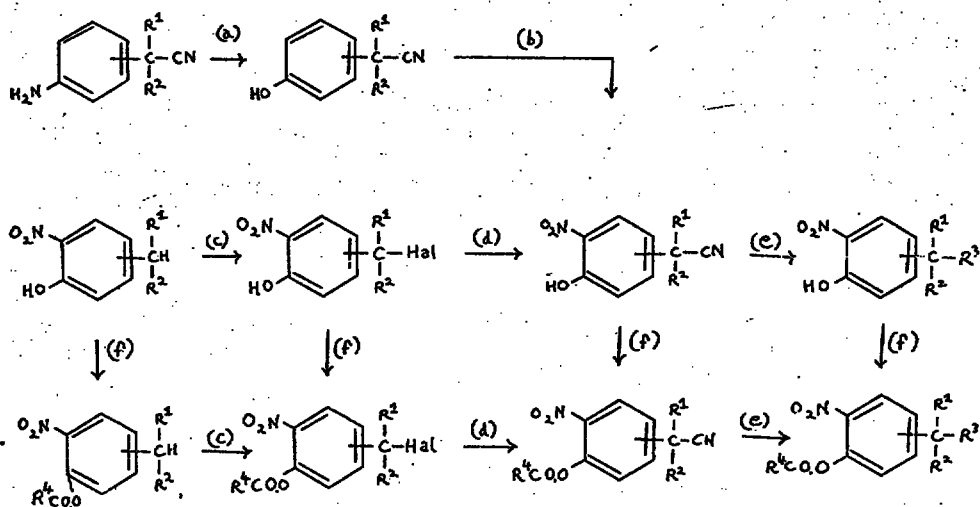
An acid of formula I may be salified by treatment with an appropriate base such as an ammonium, alkylammonium, aralkylammonium, aluminium, alkali metal or alkaline earth metal hydroxide and of course a salt of formula I may readily be converted to the free acid by treatment with an acid such as hydrochloric or sulphuric acid. An acid of formula I or a salt thereof may be converted to an ester by treatment with an appropriate alcohol or by treatment with a halide of the appropriate ester moiety or a salt of that halide if the ester moiety contains a basic nitrogen atom. An ester of formula I may of course be hydrolysed to the corresponding acid or alcohol of formula I by treatment with a suitable hydrolytic agent such as an inorganic base or acid. An acid of formula I or an ester thereof may also be converted to an amide of formula I by reaction with ammonia or an appropriate primary or secondary amine.

A resultant compound of formula I in which R^1 and/or R^2 is hydrogen may be alkylated to produce the corresponding compound of formula I in which R^1 and/or R^2 is C_{1-6} alkyl. The alkylation may be carried out by interaction of an alkali metal derivative of the appropriate benzoxazole derivative with an alkyl halide such as, for example, methyl or ethyl iodide.

Finally, in a situation where it may prove difficult by the above route to produce a compound of formula I in which both R^4 and $-CR^1R^2R^3$ have the desired meanings, a compound of formula I in which R^4 is not the desired group may be prepared, the oxazole ring in the resultant compound is then cleaved in such a way as to regenerate a compound of formula III in which X is hydrogen and Y is H_2N- , for example by cleavage with concentrated hydrochloric acid at a temperature of around $150^\circ C$, and the resultant compound of formula III is re-cyclised in the presence of a cyclising agent which will donate the required group R^4 .

The compounds of formula III above may be prepared by reducing the corresponding nitro compounds in the case where a compound of formula III in which $Y=H_2N-$ is required, followed by acylation of a resulting compound in which X is hydrogen and Y is H_2N- or treatment of the latter compound with the aldehyde R^4CHO to produce a compound of formula III in which Y is the group $R^4CO-NH-$ or $R^4CH=N-$ respectively.

The following reaction scheme shows the preparation of the above mentioned nitro intermediates from known or readily prepared chemicals, the term "Hal" representing a halogen atom and the group R^3 being as defined above except a nitrile group:—



In the above scheme, step (a) is accomplished by diazotisation followed by treatment of the resultant diazonium compound with dilute sulphuric acid. Step (b) is

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repre-
nitrite

$$\begin{array}{c} R^2 \\ | \\ -C-R^3 \\ | \\ R^2 \end{array}$$

$$\begin{array}{c} R^2 \\ | \\ -C-R^3 \\ | \\ R^2 \end{array}$$

treat-
(b) is

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carried out by nitration, for example by addition of nitric acid to a solution of the nitrile in glacial acetic acid. Steps (c) and (d) are as described above in connection with the conversion of $R^3=H \rightarrow R^3=Halogen \rightarrow R^3=CN$. Various nitrile transformation reactions (step e)) have been previously described. Step (f) is accomplished by conventional acylation using an appropriate acylating agent such as an acyl halide or acid anhydride.

The compounds of formula I above in which R³ is a nitrile or halogen radical are, as can be seen from the foregoing description, useful as intermediates for conversion to other compounds of formula I. These other compounds, i.e. where R³ is carboxy or a salt, ester, amide or hydroxamic acid derivative thereof, or is hydroxymethyl or an ester derivative thereof, including such compounds in which R⁴ is a 3-alkyl-4-hydroxyphenyl or a 3,5-dialkyl-4-hydroxyphenyl group, are useful in that they are pharmacologically active. In particular, these compounds have been shown to have low toxicity and to possess analgesic, antipyretic and/or anti-inflammatory activity as well as possessing in certain cases the ability to inhibit prostaglandin synthesis or release.

The foregoing activities have been demonstrated in tests carried out in animals usually at doses of from 0.1 to 250 mg/kg. In the treatment of humans, the dose administered may be, for example, between 0.1 and 25 mg./kg. but, of course, doses outside this range may be used at the discretion of the physician treating the patient. The pharmacologically active compounds of formula I may be administered by the enteral or parenteral routes and for this purpose they will normally be formulated into pharmaceutical compositions comprising the active ingredient in association with at least one pharmaceutically acceptable carrier therefor. Such compositions form a part of this invention and will normally consist of the active ingredient mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated by a carrier in the form of a capsule, sachet, cachet or other container. The carrier may be a solid, semi-solid or liquid material which serves as a vehicle, excipient, coating agent, or medium for the active ingredient. Some examples of the carriers which may be used are lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium phosphate, liquid paraffin, cocoa butter, oil of theobroma, alginates, tragacanth, gelatin, methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl cellulose acetate phthalate, low viscosity acetyl cellulose acetate, paraffin wax, mineral wax, vegetable wax, vegetable gum, silicone rubbers such as liquid polydimethylsiloxane rubber, plasticised or unplasticised polyvinyl chloride, plasticised polyethylene terephthalate, modified collagen, cross-linked hydrophilic polyether gel, cross-linked polyvinyl alcohol or cross-linked partially hydrolysed polyvinyl acetate.

Advantageously the compositions of the invention are formulated in a dosage unit form containing from 1 to 1000 mg. (preferably 25 to 500 mg.) of the active ingredient. Examples of suitable dosage unit forms are tablets, hard or soft gelatin capsules, microcapsules and suppositories as well as drug dispensing systems comprising the active ingredient contained in a flexible, imperforate polymeric material through which the drug may be released slowly by diffusion. More generally, the term "dosage unit form" as used herein means a physically discrete unit containing the active ingredient, generally in admixture with and/or enclosed by a pharmaceutical carrier, the quantity of active ingredient being such that one or more units are normally required for a single therapeutic administration.

In addition to the active ingredient of formula I, the compositions of the present invention may also contain one or more pharmacologically active ingredients, for example, acetylsalicylic acid and salts thereof, caffeine, codeine phosphate, phenylbutazone, paracetamol, dextropropoxyphene and indomethacin.

The compositions of the present invention will of course be adapted to the particular route of administration. Thus, for oral administration, tablets, pills, capsules, solutions or suspensions may be used; for parenteral administration, sterile injection solutions or suspensions may be used; for rectal administration, suppositories may be used; and for topical administration, creams, lotions or ointments may be used. Any of the foregoing compositions may, of course, be formulated in delayed or sustained release form in a manner well known in the art.

The following examples will further illustrate the invention.

EXAMPLE 1

2-(2-Phenyl-5-benzoxazolyl)propionic acid

(a) 2-(4-Hydroxyphenyl)propionitrile

Finely ground 2-(4-aminophenyl)propionitrile (73 g., 0.5 mole) was suspended in concentrated hydrochloride acid (125 ml.). The stirred suspension was diazotised at 0—5°C by the dropwise addition of a solution of sodium nitrite (36.23 g., 0.525 mole)

in water (60 ml.) during 1—2 hours. The almost clear solution was stirred for a further 20 minutes at 5—10°C, and then poured into a stirred, boiling solution of concentrated sulphuric acid (250 ml.) in water (2.5 l.). After 6 minutes it was cooled in an ice-bath, and then extracted with ether (×4). The combined ether extracts were extracted with 2N-sodium hydroxide solution (×6). The combined alkaline extracts were cooled in an ice-bath, acidified with concentrated hydrochloric acid and extracted with ether (×3). The combined ether extracts were washed with saturated sodium chloride solution (×3), dried (Na₂SO₄) and evaporated to leave a dark brown oil (66.7 g.) which on distillation gave 2-(4-hydroxyphenyl)propionitrile (59.58 g.), b.p. 112—122°C/0.125 m.m., m.p. 41—46°C.

Analysis: Calculated: C: 73.44, H: 6.16, N: 9.51
Found: C: 73.19, H: 5.91, N: 9.31.

(b) 2-(3-Nitro-4-hydroxyphenyl)propionitrile

A solution of 2-(4-hydroxyphenyl)propionitrile (7.79 g., 0.053 mole.) in glacial acetic acid (10 ml.) was added at 7—10°C, with stirring, to 12 N-nitric acid (8 ml.) during 45 minutes. A further volume (10 ml.) of glacial acetic acid was added during this period. The resulting yellow suspension was stirred for a further 30 minutes at 7—10°C, and then for 30 minutes at -10°C to -15°C. The suspension was diluted with water (approx. 90 ml.). Filtration yielded 2-(3-nitro-4-hydroxyphenyl)propionitrile as a yellow solid (8.43 g.), m.p. 78—81°C.

Analysis: Calculated: C: 56.24, H: 4.19, N: 14.57
Found: C: 56.29, H: 4.24, N: 14.47

(c) (i) 2-(3-Amino-4-hydroxyphenyl)propionitrile

2-(3-Nitro-4-hydroxyphenyl)propionitrile (123.8 g., 0.64 mole.) was suspended in absolute ethanol (950 ml.) and added during 20 minutes, with cooling, to a solution of stannous chloride dihydrate (437.8 g., 1.94 mole.) in concentrated hydrochloric acid (591 ml., 7 mole.). The addition was made at such a rate that the temperature of the reaction mixture did not exceed 20°C. Stirring of the mixture was continued for a further 19 hours at room temperature. The resulting solution, together with ice (1.75 kg.) was added during one hour to a cooled solution of sodium hydroxide (650 g.) in water (600 ml.). The temperature of the reaction mixture was maintained at 15—20°C during the addition. The mixture was stirred for a further 1 hour, and the pH then adjusted to 6 by the addition of concentrated hydrochloric acid. The resulting suspension was filtered and the filtrate saturated with sodium chloride, and then extracted with ether (×6). The combined ether extracts were dried (Na₂SO₄) and evaporated to leave a solid (69.15 g.) which was suspended in chloroform and extracted with 2N-hydrochloric acid (×6). The combined acid extracts were neutralised to pH 7—8 by the addition of sodium bicarbonate. The resulting suspension was extracted with ether (×4). The combined ether extracts were washed twice with water, dried (Na₂SO₄), and evaporated to yield 2-(3-amino-4-hydroxyphenyl)propionitrile as a light brown solid (62.85 g.), m.p. 110—112°C.

Analysis: Calculated: C: 66.64, H: 6.21, N: 17.27
Found: C: 66.45, H: 6.09, N: 16.99

(c) (ii) 2-(3-Amino-4-hydroxyphenyl)propionitrile was also prepared by the following method:—

2-(3-Nitro-4-hydroxyphenyl)propionitrile (38.4 g., 0.2 mole.) was suspended in absolute ethanol (250 ml.) and hydrogenated at 4 atmospheres pressure and room temperature over 10% palladium on charcoal. Hydrogenation was complete in 3.8 hours. The catalyst was removed by filtration. Evaporation of the filtrate yielded 2-(3-amino-4-hydroxyphenyl)propionitrile (17 g.), m.p. 110°C.

(d) 2-(3-Benzamido-4-hydroxyphenyl)propionitrile

Benzoyl chloride (27.09 g., 0.19 mole.) was added, with cooling, during 20 minutes to a stirred solution of 2-(3-amino-4-hydroxyphenyl)propionitrile (28.35 g., 0.175 mole.) in dry pyridine (200 ml.) at 0—3°C. After addition was complete, the mixture was heated at 100°C, for 1 hour. It was then evaporated under reduced pressure to yield crude 2-(3-benzamido-4-hydroxyphenyl)propionitrile as an oil.

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5	(e) 2-(2-Phenyl-5-benzoxazolyl)propionitrile The oil from (d) above was boiled for 30 minutes, during which time the temperature of the vapour above the oil rose to 130°C. On cooling the residue solidified. Recrystallisation of the solid from methanol yielded 2-(2-phenyl-5-benzoxazolyl)propionitrile (27.65 g.), m.p. 118—120°C.	5
	Analysis: Calculated: C: 77.39, H: 4.87, N: 11.28 Found: C: 77.33, H: 5.11, N: 11.34	
10	(f) 2-(2-Phenyl-5-benzoxazolyl)propionic acid A solution of 2-(2-phenyl-5-benzoxazolyl)propionitrile (24 g., 0.096 mole.) in concentrated hydrochloric acid (220 ml.) was refluxed for 2.5 hours. The mixture was poured into ice/water (1 litre). The precipitated 2-(2-phenyl-5-benzoxazolyl)propionic acid was filtered off and washed well with water. The dry acid weighed 23 g. and had m.p. 177—179°C.	10
15	Analysis: Calculated: C: 71.89, H: 4.90, N: 5.24 Found: C: 72.13, H: 4.95, N: 5.39	15
EXAMPLE 2		
In a similar manner to that of Example 1, the following compounds were synthesised:		
20	(a) 2-(2- <i>p</i> -Fluorophenyl-5-benzoxazolyl)propionic acid, m.p. 162—164°C.	20
	Analysis: Calculated: C: 67.36, H: 4.24, N: 4.91 Found: C: 67.58, H: 4.45, N: 5.07	
25	(b) 2-(2- <i>p</i> -Chlorophenyl-5-benzoxazolyl)propionic acid, m.p. 188—191°C.	25
	Analysis: Calculated: C: 63.68, H: 4.00, N: 4.64 Found: C: 63.50, H: 4.16, N: 4.72	
30	(c) 2-(2- <i>m</i> -Chlorophenyl-5-benzoxazolyl)propionic acid, m.p. 173—175°C	25
	Analysis: Calculated: C: 63.68, H: 4.00, N: 4.64 Found: C: 63.50, H: 4.01, N: 4.75	
35	(d) 2-(2- <i>p</i> -Methylphenyl-5-benzoxazolyl)propionic acid, m.p. 166—168°C.	30
	Analysis: Calculated: C: 72.58, H: 5.37, N: 4.97 Found: C: 72.36, H: 5.46, N: 5.4	
40	(e) 2-(2- <i>m</i> -Methylphenyl-5-benzoxazolyl)propionic acid, m.p. 155—157°C.	35
	Analysis: Calculated: C: 72.58, H: 5.37, N: 4.97 Found: C: 72.39, H: 5.61, N: 5.14	
45	(f) 2-(2- <i>o</i> -Methylphenyl-5-benzoxazolyl)propionic acid, m.p. 107—110°C.	35
	Analysis: Calculated: C: 72.58, H: 5.37, N: 4.97 Found: C: 72.54, H: 5.59, N: 4.77	
50	(g) 2-(2- <i>p</i> -Methoxyphenyl-5-benzoxazolyl)propionic acid, m.p. 189—191°C.	40
	Analysis: Calculated: C: 68.67, H: 5.08, N: 4.71 Found: C: 68.42, H: 5.36, N: 4.72	
55	(h) 2-(2- <i>o</i> -Hydroxy- <i>p</i> -chlorophenyl-5-benzoxazolyl)propionitrile, m.p. 143—145°C (with prior softening).	40
	Analysis: Calculated: C: 64.3, H: 3.7, N: 9.4 Found: C: 64.1, H: 3.5, N: 9.5	

(i) 2-(2-*o*-Hydroxy-*p*-chlorophenyl-5-benzoxazolyl)propionic acid, m.p. 197—200°C.

Analysis: Calculated: C: 60.5, H: 3.8, N: 4.4
Found: C: 60.65, H: 4.06, N: 4.5

(j) 2-(2-*p*-Chlorophenyl-5-benzoxazolyl)propionitrile, m.p. 150—153°C.

Analysis: Calculated: C: 67.96, H: 3.92, N: 9.90
Found: C: 67.57, H: 3.96, N: 9.25

(k) 2-(2-*p*-Acetylphenyl-5-benzoxazolyl)propionic acid, m.p. 207—209°C.

Analysis: Calculated: C: 69.90, H: 4.85, N: 4.53
Found: C: 69.72, H: 4.75, N: 4.50

EXAMPLE 3

(a) 2-(2-*p*-Bromophenyl-5-benzoxazolyl)propionic acid, one third hydrochloride
This compound was prepared using the procedure described in Example 1. The product, m.p. 195—197°C, contained one third of a molecule of hydrogen chloride.

Analysis: Calculated: C: 53.60, H: 3.46, N: 3.90
Found: C: 53.25, H: 3.37, N: 3.88

(b) 2-(2-*p*-Bromophenyl-5-benzoxazolyl)propionic acid, sodium salt
2-(2-*p*-Bromophenyl-5-benzoxazolyl)propionic acid, one third hydrochloride (4.3 g., 0.012 mole.) was ground in 1N-sodium hydroxide solution (20 ml.). To the suspension was added an equal volume of chloroform. The suspension was stirred, and then filtered. Recrystallisation of the solid from aqueous ethanol yielded 2-(2-*p*-bromophenyl-5-benzoxazolyl)propionic acid, sodium salt, m.p. >316°C.

Analysis: Calculated: C: 52.19, H: 3.01, N: 3.8
Found: C: 51.99, H: 3.17, N: 4.07

EXAMPLE 4

Ethyl 2-(2-phenyl-5-benzoxazolyl)propionate

2-(2-Phenyl-5-benzoxazolyl)propionic acid (10 g., 0.037 mole.) and toluene-*p*-sulphonic acid (0.5 g.) were dissolved in a mixture of benzene (60 ml.) and absolute ethanol (25 ml.). The solution was refluxed for 12 hours. After cooling the solution was washed twice with 2N-sodium hydroxide solution, and then several times with water. After drying (Na₂SO₄) it was evaporated under reduced pressure to leave ethyl 2-(2-phenyl-5-benzoxazolyl)propionate (8 g.) as an oil, which solidified on cooling, m.p. 45—46°C.

Analysis: Calculated: C: 73.20, H: 5.80, N: 4.74
Found: C: 72.95, H: 5.51, N: 4.79

In a similar manner, the following compound was prepared:

Ethyl 2-(2-*p*-chlorophenyl-5-benzoxazolyl)propionate, m.p. 59—62°C.

Analysis: Calculated: C: 65.54, H: 4.89, N: 4.24
Found: C: 65.46, H: 4.85, N: 4.11

EXAMPLE 5

2-(2-Phenyl-5-benzoxazolyl)propyl alcohol

An approximately 1M-solution (15 ml.) of diborane in dry tetrahydrofuran was added during 5 minutes to a stirred suspension of 2-(2-phenyl-5-benzoxazolyl)propionic acid (3 g., 0.011 mole.) in dry tetrahydrofuran (10 ml.) at room temperature. The resulting solution was stirred for 3.75 hours at room temperature, and then poured onto crushed ice (35 g.) containing concentrated hydrochloric acid (75 ml.). The mixture was extracted with chloroform (×2). The combined chloroform extracts were washed twice with a saturated sodium bicarbonate solution, dried (Na₂SO₄), and evaporated under reduced pressure to give hydrated 2-(2-phenyl-5-benzoxazolyl)propyl alcohol (2.56 g.) as a solid, m.p. 99—103°C.

Analysis: Calculated (for C₁₆H₁₅NO₂·4H₂O)

Found: C: 74.53, H: 6.05, N: 5.43
C: 74.74, H: 5.95, N: 5.41

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	EXAMPLE 6	
	2-Phenyl-5-benzoxazolyl-acetic acid	
5	A solution of 2-phenyl-5-benzoxazolylacetonitrile (8.9 gm.)—prepared by the method described in Example 1(e)—in concentrated hydrochloric acid (80 ml.) was heated on a steam bath for 2.5 hours. The solution was then diluted with ice/water and allowed to stand. The solid produced was crystallised from toluene to give white crystals of 2-phenyl-5-benzoxazolyl-acetic acid, m.p. 175°C.	5
	Analysis: Calculated (for $C_{15}H_{11}NO_3$)	
10	Found: C: 71.1, H: 4.4, N: 5.5 C: 71.0, H: 4.4, N: 5.6	10
	EXAMPLE 7	
	2-Phenyl-6-benzoxazolyl-acetic acid	
15	(a) 6-Methyl-2-phenylbenzoxazole	15
20	Benzoyl chloride (79 ml) was slowly added to a stirred suspension of 6-amino-3- <i>m</i> -cresol (83 gm) in pyridine (600 ml). The temperature was kept below 5°C. The solution was heated under reflux for 2 hr., and then was evaporated to dryness to give an oil. This oil was extracted with aqueous 2N sodium hydroxide solution. The aqueous layer was made acid with concentrated hydrochloric acid. The solid, 2'-hydroxy-4'-methylbenzanilide, m.p. 170°C, was filtered off. This product was heated until no more water was evolved. The resulting liquid was allowed to cool and the solid produced was powdered and taken up in petroleum ether. The solution was treated with carbon and the filtrate evaporated to dryness to yield 6-methyl-2-phenylbenzoxazole, m.p. 93°C.	20
25	(b) 6-Bromomethyl-2-phenylbenzoxazole	25
30	N-Bromosuccinimide (25.9 gm) was added to a cold solution of 6-methyl-2-phenylbenzoxazole (30 gm) in carbon tetrachloride (250 ml). Benzoyl peroxide (500 mg) was added and the mixture was heated under reflux for 3 hr. in the presence of u.v. light. The solid residue was filtered off. The filtrate was evaporated down slightly, treated with carbon and allowed to cool. The crystals which were formed were recrystallised from benzene to yield 6-bromomethyl-2-phenylbenzoxazole, m.p. 162°C.	30
35	(c) 2-Phenyl-6-benzoxazolylacetonitrile	35
	A mixture of 6-bromomethyl-2-phenylbenzoxazole (40 gm) and sodium cyanide (7.4 gm.) in dry dimethylformamide (800 ml) was heated on a steam bath for 3 hr. The mixture was filtered and the filtrate was evaporated to dryness. The solid was recrystallised to give 2-phenyl-6-benzoxazolylacetonitrile as white crystals, m.p. 144°C.	
40	(d) 2-Phenyl-6-benzoxazolylacetic acid	40
	A solution of 2-phenyl-6-benzoxazolylacetonitrile (11 gm) in conc. hydrochloric acid (100 ml) was heated on a steam bath for 1 hr. The solution was then allowed to cool. The resultant solid was filtered off and equilibrated between aqueous sodium bicarbonate solution and chloroform. The aqueous layer was made acid with hydrochloric acid and was extracted with chloroform. The chloroform solution was evaporated to dryness. The residue was recrystallised from toluene to give white crystals of 2-phenyl-6-benzoxazolylacetic acid, m.p. 170°C.	
45	Analysis found: C. 71.0, H: 4.4, N: 5.5% $C_{15}H_{11}NO_3$ requires: C: 71.1, H: 4.4, N: 5.4%.	45
	EXAMPLE 8	
	Ethyl 2-phenyl-6-benzoxazolyl acetate	
50	A solution of 2-phenyl-6-benzoxazolylacetic acid (20 gm) in ethanol (200 ml) was heated under reflux for 6 hr., during which time dry hydrogen chloride gas was passed through the solution. The residual oil obtained on evaporation of the solution was extracted with ether and this solution was evaporated to dryness. The solid formed was recrystallised from toluene/petroleum ether to yield white crystals of ethyl 2-phenyl-6-benzoxazolyl acetate, m.p. 76°C.	50
55	Analysis found: C: 72.3, H: 5.4, N: 4.8 $C_{17}H_{15}NO_3$ requires: C: 72.6, H: 5.4, N: 5.0.	55

EXAMPLE 9

Ethyl 2-(2-Phenyl-6-benzoxazolyl)propionate

5 A solution of ethyl 2-phenyl-6-benzoxazolyl acetate (34 gm) in ether (200 ml) was added to a stirred solution of NaNH_2 (from 3.2 gm sodium) in liquid ammonia (500 ml). This red mixture was stirred for 15 min., and then a solution of methyl iodide (8.5 ml) in ether (10 ml) was added rapidly. When the reaction mixture appeared colourless the reaction was stopped by the addition of excess ammonium chloride. The mixture was evaporated to dryness and the residue was extracted with ether. The etheral solution was evaporated to dryness to yield white crystals of ethyl 2-(2-phenyl-6-benzoxazolyl)propionate, m.p. 46°C .

Analysis Found: C: 73.0, H: 5.7, N: 5.0
 $\text{C}_{18}\text{H}_{17}\text{NO}_3$ requires: C: 73.2, H: 5.8, N: 4.7.

EXAMPLE 10

2-(2-Phenyl-6-benzoxazolyl)propanol

15 A solution of lithium aluminium hydride (~ 2 gm) in ether (50 ml) was slowly added to a solution of ethyl 2-(2-phenyl-6-benzoxazolyl)propionate (5 g) in ether (40 ml). The mixture was heated under reflux for 1 hr., and then ethyl acetate was slowly added until effervescence ceased. 6 N-Aqueous hydrochloric acid was then added and the ether layer was separated off and dried. Chromatography over silica gel yield pure 2-(2-phenyl-6-benzoxazolyl)propanol, m.p. 98°C .

Analysis found: C: 76.0, H: 5.8, N: 5.6
 $\text{C}_{18}\text{H}_{19}\text{NO}_2$ requires: C: 75.9, H: 6.0, N: 5.5.

EXAMPLE 11

2-(2-Phenyl-6-benzoxazolyl)propionamide

25 A mixture of ethyl 2-(2-phenyl-6-benzoxazolyl)propionate (4.4 g) and ammoniacal glycerol (40 ml) was heated at 150°C in a bomb for 18 hr. The mixture was diluted twofold with water, and the resultant white solid was filtered off and recrystallised from ethyl acetate to give white crystals of 2-(2-phenyl-6-benzoxazolyl)propionamide, m.p. 193°C .

30 Analysis found: C: 72.1, H: 5.4, N: 10.7
 $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2$ requires: C: 72.2, H: 5.3, N: 10.5.

By the same method, the following compounds were prepared:

(a) 2-(2-Phenyl-5-benzoxazolyl)propionamide, m.p. $202-204^\circ\text{C}$.

35 Analysis: Calculated: C: 72.2, H: 5.3, N: 10.5
 Found: C: 72.0, H: 5.1, N: 10.4

(b) 2-(2-*p*-Chlorophenyl-5-benzoxazolyl)propionamide, m.p. $245-246^\circ\text{C}$.

Analysis: Calculated: C: 63.89, H: 4.35, N: 9.31
 Found: C: 63.64, H: 4.30, N: 9.22

EXAMPLE 12

2-(2-Phenyl-6-benzoxazolyl)propionic acid

40 A solution of ethyl 2-(2-phenyl-6-benzoxazolyl)propionate (15 g) in concentrated hydrochloric acid (150 ml) was heated on a steam bath for 6 hr. The solution was cooled and the crystals which formed were filtered off. These were recrystallised from ethanol/water to yield 2-(2-phenyl-6-benzoxazolyl)propionic acid, m.p. 132°C .

45 Analysis Found: C: 71.7, H: 5.0, N: 5.3
 $\text{C}_{18}\text{H}_{15}\text{NO}_3$ requires: C: 71.9, H: 4.9, N: 5.2%.

EXAMPLE 13

2-(2-*p*-Chlorophenyl-6-benzoxazolyl)propionic acid

50 (a) 2-(3-Hydroxy-4-aminophenyl)propionic acid hydrochloride
 A solution of ethyl 2-(2-phenyl-6-benzoxazolyl)propionate (10 g) in concentrated hydrochloric acid (150 ml) was heated at 160°C for 24 hr. The resulting mixture was evaporated to dryness and the residue was taken up in water. This solution was washed

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with chloroform and then was evaporated to dryness to yield 2-(3-hydroxy-4-aminophenyl)propionic acid hydrochloride as a white powder, m.p. 170°C (dec.).

(b) Ethyl 2-(3-hydroxy-4-aminophenyl)propionate

A solution of 2-(3-hydroxy-4-aminophenyl)propionic acid hydrochloride (5 g) in ethanol (100 ml) was saturated with hydrogen chloride and the resulting solution was heated under reflux for 6 hr. The solution was evaporated to dryness and the residue was taken up in ethanol and this solution was neutralised with sodium hydroxide solution. The residue obtained on evaporation was taken up in chloroform and the solution was washed with water. Evaporation of the chloroform solution yielded ethyl 2-(3-hydroxy-4-aminophenyl)propionate, m.p. 114—5°C.

Analysis found: C: 63.2, H: 7.2, N: 6.9
C₁₁H₁₃NO₃ requires: C: 63.1, H: 7.2, N: 6.7.

(c) Ethyl 2-(2-*p*-chlorophenyl-6-benzoxazolyl)propionate

A solution of ethyl (3-hydroxy-4-aminophenyl)propionate (2.5 g) in pyridine (15 ml) was treated with *p*-chlorobenzoyl chloride (1.65 ml) at 5°C. After stirring for 2 hr. at room temperature the solution was evaporated to dryness.

The residue was heated at 220°C until no more water was evolved, and then was allowed to cool. This yielded ethyl 2-(2-*p*-chlorophenyl-6-benzoxazolyl)propionate.

(d) 2-(2-*p*-Chlorophenyl-6-benzoxazolyl)propionic acid

A solution of ethyl 2-(2-*p*-chlorophenyl-6-benzoxazolyl)propionate (4 g) in aqueous sodium hydroxide (30 ml) was heated on a steam bath for ½ hr. On cooling the black solution was washed with chloroform. On acidification of the black solution with hydrochloric acid the mixture was extracted with chloroform. This solution on evaporation yielded 2-(2-*p*-chlorophenyl-6-benzoxazolyl)propionic acid, m.p. 196°C.

Analysis found: C: 63.9, H: 4.2, N: 4.8, Cl: 12.0
C₁₆H₁₂ClNO₃ requires: C: 63.7, H: 4.0, N: 4.6, Cl: 11.8

In a similar manner, the following compounds were prepared:

(a) Ethyl 2-[2-(3,4-methylenedioxyphenyl)-5-benzoxazolyl]propionate, m.p. 76—79°C.

Analysis: Calculated: C: 67.25, H: 5.0, N: 4.1
Found: C: 67.1, H: 5.05, N: 4.4

(b) 2-[2-(3,4-Methylenedioxyphenyl)-5-benzoxazolyl]propionic acid, m.p. 185—188°C.

Analysis: Calculated: C: 65.5, H: 4.2, N: 4.5
Found: C: 65.4, H: 3.9, N: 4.7

(c) 2-[2-(3,4-Dichlorophenyl)-5-benzoxazolyl]propionic acid, m.p. 169—173°C.

Analysis: Calculated: C: 57.1, H: 3.3, N: 4.2
Found: C: 56.9, H: 3.4, N: 4.1

(d) 2-[2-(2,4-Dichlorophenyl)-5-benzoxazolyl]propionic acid, m.p. 151—153°C.

Analysis: Calculated: C: 57.1, H: 3.3, N: 4.2
Found: C: 57.1, H: 3.3, N: 4.4

(e) Ethyl 2-(2-*p*-methylsulphonylphenyl-5-benzoxazolyl)propionate, m.p. 141—142°C.

Analysis: Calculated: C: 61.1, H: 5.1, N: 3.75
Found: C: 61.2, H: 5.1, N: 3.6

(f) 2[2-(2-Furyl)-5-benzoxazolyl]propionic acid, m.p. 160—162°C.

Analysis: Calculated: C: 65.4, H: 4.3, N: 5.4
Found: C: 65.3, H: 4.4, N: 5.4

(g) 2-(2-Cyclohexyl-5-benzoxazolyl)propionic acid, m.p. 115—117°C.

Analysis: Calculated: C: 70.30, H: 7.00, N: 5.12
Found: C: 70.58, H: 6.86, N: 5.35

(h) 2-(2-*m*-Trifluoromethylphenyl-5-benzoxazolyl)propionic acid, m.p. 144—147°C.

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Analysis: Calculated: C: 60.89, H: 3.60, N: 4.17
Found: C: 61.05, H: 3.87, N: 4.41

5

(i) 2-[2-(2-Thienyl)-5-benzoxazolyl]propionic acid, m.p. 161—163°C.

Analysis: Calculated: C: 61.52, H: 4.05, N: 5.12
Found: C: 61.72, H: 4.19, N: 5.07

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(j) 2-(2-*o*-Chlorophenyl-5-benzoxazolyl)propionic acid, m.p. 101—103°C.

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Analysis: Calculated: C: 63.68, H: 4.01, N: 4.64
Found: C: 63.80, H: 4.22, N: 4.82

(k) 2-(2-*p*-Trifluoromethylphenyl-5-benzoxazolyl)propionic acid, m.p. 165—168°C.

15

Analysis: Calculated: C: 60.89, H: 3.60, N: 4.17
Found: C: 60.76, H: 3.38, N: 4.34

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(l) 2-(2-*p*-Iodophenyl-5-benzoxazolyl)propionic acid, m.p. 205—208°C.

Analysis: Calculated: C: 48.87, H: 3.07, I: 32.27, N: 3.56
Found: C: 48.91, H: 2.93, I: 32.51, N: 3.26

(m) 2-(2-*m*-Fluorophenyl-5-benzoxazolyl)propionic acid, m.p. 135—141°C.

20

Analysis: Calculated: C: 67.36, H: 4.24, N: 4.91
Found: C: 67.46, H: 4.37, N: 5.11

20

(n) 2-[2-(3,5-Dichlorophenyl)-5-benzoxazolyl]propionic acid, m.p. 161—165°C.

Analysis: Calculated: C: 57.16, H: 3.29, N: 4.16
Found: C: 57.13, H: 3.51, N: 4.22

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(o) 2-(2-*o*-Fluorophenyl-5-benzoxazolyl)propionic acid, m.p. 180—183°C.

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Analysis: Calculated: C: 67.36, H: 4.24, N: 4.91
Found: C: 67.16, H: 4.50, N: 4.91

(p) 2-(2-*p*-Fluorophenyl-6-benzoxazolyl)propionic acid, m.p. 147°C.

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Analysis: Calculated: C: 67.4, H: 4.2, N: 4.9, F: 6.7
Found: C: 67.2, H: 4.4, N: 4.9, F: 6.8

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(q) 2-(2-*p*-Chlorophenyl-5-benzoxazolyl)propionic acid, m.p. 188—191°C.

Analysis: Calculated: C: 63.68, H: 4.00, N: 4.64
Found: C: 63.50, H: 4.16, N: 4.72

EXAMPLE 14

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2-(2-*o*-Chlorophenyl-6-benzoxazolyl)propionic acid

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(a) Ethyl 2-(2-*o*-chlorophenyl-6-benzoxazolyl)propionate

A solution of *o*-chlorobenzaldehyde (4.3 g.) and ethyl 2-(3-hydroxy-4-amino-phenyl)propionate (6 g.) in toluene (100 ml.) was heated, using a Dean and Stark apparatus to collect the water formed. After 30 minutes the solution was evaporated to dryness.

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The residue was dissolved in acetic acid (100 ml.), lead tetraacetate (15 g.) was added and the solution was heated on a steam bath for 1 hour. The solution was poured

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into ice/water and extracted with ether to give the oil, ethyl 2-(2-*o*-chlorophenyl-6-benzoxazolyl)propionate, a sample of which gave a satisfactory micro-analysis.

(b) 2-(2-*o*-Chlorophenyl-6-benzoxazolyl)propionic acid

The ethyl 2-(2-*o*-chlorophenyl-6-benzoxazolyl)propionate from (a) was stirred with sodium hydroxide solution (50 ml.). After 1½ hours the solution was evaporated to dryness. Acidification and re-crystallisation from ether gave 2-(2-*o*-chlorophenyl-6-benzoxazolyl)propionic acid, m.p. 108—110°C.

Analysis found: C: 63.5, H: 4.1, N: 4.8, Cl: 12.0
C₁₆H₁₂ClNO₃ requires: C: 63.7, H: 4.0, N: 4.6, Cl: 11.8

EXAMPLE 15

2-[2-(3-Pyridyl)-5-benzoxazolyl]propionic acid

Sodium (0.115 g.) was dissolved carefully in methanol (45 ml.) and 3-cyanopyridine (5.2 g.) was added. Next day, acetic acid (0.3 g.) was added, followed by 2-(3-amino-4-hydroxyphenyl)propionic acid (9.05 g.). The stirred mixture was heated under reflux for 5 hours. The solid dissolved completely during this time. An equal volume of water was added to the hot solution. On cooling, cream crystals separated and were filtered off and re-crystallised from dimethylformamide-ethanol to yield the desired acid, m.p. 197—200°C.

Analysis: Calculated: C: 67.2, H: 4.5, N: 10.4
Found: C: 67.3, H: 4.3, N: 10.3

In the same way, the following compounds were prepared:

(a) 2-[2-(4-Pyridyl)-5-benzoxazolyl]propionic acid, m.p. 247—250°C.

Analysis: Calculated: C: 67.2, H: 4.5, N: 10.4
Found: C: 66.9, H: 4.8, N: 10.2

(b) 2-[2-(2-Pyridyl)-5-benzoxazolyl]propionic acid, m.p. 177—179°C.

Analysis: Calculated: C: 67.2, H: 4.5, N: 10.4
Found: C: 67.0, H: 4.5, N: 10.2

(c) 2-(2-*p*-Chlorophenyl-5-benzoxazolyl)propionic acid, m.p. 188°C.

Analysis: Calculated: C: 63.68, H: 4.00, N: 4.64
Found: C: 63.50, H: 4.16, N: 4.72

EXAMPLE 16

N,N-Diethyl-2-(2-phenyl-5-benzoxazolyl)propionamide

2-(2-Phenyl-5-benzoxazolyl)propionic acid (50 g.) and thionyl chloride (20 ml.) were heated together on a steam bath for 20 minutes. The excess of thionyl chloride was removed by evaporation under reduced pressure. The residue was cooled to 0°C. and treated cautiously with an excess of diethylamine. After 1 hour the reaction mixture was equilibrated between water (100 ml.) and ether (100 ml.). The ether layer was washed three times with water (50 ml.), dried (Na₂SO₄), and evaporated. The residue was chromatographed on silica gel and then re-crystallised from a small volume of ethanol to yield the required diethylamide, m.p. 108—110°C.

Analysis: Calculated: C: 74.5, H: 6.8, N: 8.7
Found: C: 74.6, H: 6.6, N: 8.7

EXAMPLE 17

2-(2-Phenyl-5-benzoxazolyl)propionylhydroxamic acid

A solution of sodium (0.16 g.) in absolute ethanol (5 ml.) was added to a solution of hydroxylamine hydrochloride (0.46 g.) in absolute ethanol (12 ml.). The chilled mixture was filtered and a solution of ethyl 2-(2-phenyl-5-benzoxazolyl)propionate (2.0 g.) in ethanol (10 ml.) was added to the filtrate. On standing at room temperature for 3 days, a precipitate formed and was filtered off. The solid was stirred in aqueous acetic acid and filtered off, dried, and re-crystallised from dimethylformamide-ethanol.

The resulting white crystals of the desired hydroxamic acid melted at 204—205°C.

Analysis: Calculated: C: 68.1, H: 5.0, N: 9.9
Found: C: 68.1, H: 5.0, N: 9.75

EXAMPLE 18

5

2-(*p*-Chlorophenyl)-5-benzoxazolylacetic acid

A suspension of ethyl 4-chlorobenzimidate hydrochloride (16.5 g.) and 3-amino-4-hydroxyphenylacetic acid (12.53 g.) in methanol (75 ml.) was refluxed for 2 hours. After standing at room temperature overnight the white solid product was removed by filtration. Re-crystallisation from ethanol gave the required acid, m.p. 241—242°C.

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Analysis: Calculated: C: 62.61, H: 3.50, N: 4.86
Found: C: 62.89, H: 3.59, N: 4.92

EXAMPLE 19

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2-(2-*p*-Chlorophenyl-5-benzoxazolyl)propionic acid, sodium salt, monohydrate
Sodium bicarbonate (1.95 g.) was added to a solution of 2-(2-*p*-chlorophenyl-5-benzoxazolyl)propionic acid (7 g.) in a mixture of methanol (100 ml.), chloroform (50 ml.) and water (60 ml.). The resulting solution was evaporated to leave a white solid. The solid was washed with chloroform (100 ml.), filtered off and dried to yield the desired sodium salt, monohydrate, m.p. 312—314°C.

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Analysis: Calculated: C: 56.23, H: 3.83, N: 4.09
Found: C: 56.65, H: 3.50, N: 3.99

EXAMPLE 20

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2-(2-Phenyl-5-benzoxazolyl)isobutyric acid

By treatment of 2-(2-phenyl-5-benzoxazolyl)propionitrile with methyl iodide in the manner described in Example 9, there was obtained 2-(2-phenyl-5-benzoxazolyl)isobutyronitrile which, on treatment with concentrated hydrochloric acid as described in Example 1(f), yielded 2-(2-phenyl-5-benzoxazolyl)isobutyric acid, m.p. 92—95°C.

Analysis: Calculated: C: 77.9, H: 5.3, N: 10.7
Found: C: 77.6, H: 5.3, N: 10.45

EXAMPLE 21

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2-[2-(3-Nitro-4-chlorophenyl)benzoxazol-5-yl]propionic acid

A solution of 3-nitro-4-chlorobenzaldehyde (0.925 g.) and 2-(3-amino-4-hydroxyphenyl)propionic acid (0.900 g.) in ethanol (25 ml.) was heated under reflux for 3.5 hours. The solution was evaporated to give a solid Schiff's base which was dissolved in hot acetic acid (50 ml.). Lead tetraacetate (2.8 g.) was added and the reaction mixture was allowed to cool to room temperature. Next morning, water (200 ml.) was added which resulted in the deposition of a sticky solid. The latter was dried and triturated with a small amount of chloroform to yield the pure benzoxazole acid (0.5 g.), m.p. 210—213°C.

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Analysis: Calculated: C: 55.4, H: 3.2, N: 8.1
Found: C: 55.2, H: 3.2, N: 8.05

In a similar manner, the following compound was prepared:

2-(2-*p*-Nitrophenyl-5-benzoxazolyl)propionic acid, m.p. 211—217°C.

Analysis: Calculated: C: 61.53, H: 3.87, N: 8.97
Found: C: 61.29, H: 3.75, N: 8.68

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EXAMPLE 22

2-(2-Phenyl-6-benzoxazolyl)ethanol

Ethyl 2-phenyl-6-benzoxazolylacetate, treated with lithium aluminium hydride in the manner described in Example 10, yielded 2-(2-phenyl-6-benzoxazolyl)ethanol, m.p. 89°C.

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Analysis found: C: 75.5, H: 5.6, N: 5.8
C₁₅H₁₃NO₂ requires: C: 75.3, H: 5.5, N: 5.9

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EXAMPLE 23

From the corresponding nitriles were obtained:

- 2-(3-Benzamido-4-hydroxyphenyl)propionic acid, m.p. 189—192°C.
- 2-(3-*o*-Chlorobenzamido-4-hydroxyphenyl)propionic acid, m.p. 150—157°C.
- 2-(3-*p*-Chlorobenzamido-4-hydroxyphenyl)propionic acid, m.p. 209—216°C.

On heating the foregoing compounds, there were obtained respectively:

- 2-(2-Phenyl-5-benzoxazolyl)propionic acid, m.p. 177—178°C.
- 2-(2-*o*-Chlorophenyl-5-benzoxazolyl)propionic acid, m.p. 102—103°C.
- 2-(2-*p*-Chlorophenyl-5-benzoxazolyl)propionic acid, m.p. 188—190°C.

In the following Examples of pharmaceutical compositions of the present invention, the term "medicament" is used to indicate the compound 2-(2-*p*-chlorophenyl-5-benzoxazolyl)propionic acid. That compound may of course be replaced by any other active compound of formula I and the amount of medicament may be increased or decreased depending on the degree of activity of the medicament used.

EXAMPLE 24

Tablets each containing 100 mg of medicament are made as follows:—

Medicament	100 mg
Potato starch	38 mg
Lactose	25 mg
Ethyl cellulose (as 20% solution in industrial alcohol)	2 mg
Alginic acid	7 mg
Magnesium stearate	1 mg
Talc	2 mg
Total	175 mg

The medicament, starch and lactose are passed through a No. 44 mesh B.S.S. sieve and mixed thoroughly. The solution of ethyl cellulose is mixed with the resultant powders which are then passed through a No. 12 mesh B.S.S. sieve. The granules produced are dried at 50—60°C. and then passed through a No. 16 mesh B.S.S. sieve. The alginic acid, magnesium stearate and talc, previously passed through a No. 60 mesh B.S.S. sieve, are added to the granules, mixed and compressed in a tableting machine to yield tablets each weighing 175 mg.

EXAMPLE 25

Capsules each containing 200 mg of medicament are made as follows:—

Medicament	200 mg
Lactose	48 mg
Magnesium stearate	2 mg

The medicament, lactose and magnesium stearate are passed through a No. 44 mesh B.S.S. sieve and filled into hard gelatine capsules in 250 mg quantities.

EXAMPLE 26

Injection solutions each containing 100 mg of medicament per 5 ml solution are made as follows:—

Medicament	100 mg
Sodium hydroxide (10% solution)	q.s.
Water for injection	to 5 ml

The medicament is suspended in the water and the sodium hydroxide solution added drop by drop with stirring until the medicament is in solution. The pH of the solution is adjusted to between 8.0 and 8.5, the solution is sterilised by filtration through a bacteria-proof filter and filled into previously sterilised glass ampoules, which are then hermetically sealed under aseptic conditions.

EXAMPLE 27

Suppositories each containing 250 mg of medicament are made as follows:—

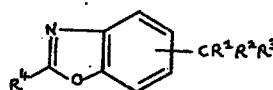
Medicament
Theobroma Oil

250 mg
to 2000 mg

- 5 The medicament is passed through a No. 60 mesh B.S.S. sieve and suspended in the theobroma oil, previously melted using the minimum of heat necessary. The mixture is then poured into a suppository mould of nominal 2 g capacity and allowed to cool.

WHAT WE CLAIM IS:—

- 10 1. Compound of the formula:



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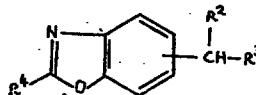
- 15 wherein the group $-CR^1R^2R^3$ is in the 5- or 6-position of the benzoxazole nucleus, R^1 and R^2 are independently hydrogen or C_{1-4} alkyl, R^3 is a nitrile group, carboxy or a salt, ester, amide or hydroxamic acid derivative thereof, or hydroxymethyl or an ester derivative thereof, and R^4 is cyclohexyl, or a heteroaryl or phenyl group optionally substituted in any available position by one or more radicals selected from C_{1-6} alkylsulphonyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, nitro, C_{2-7} acyl, hydroxy, amino, C_{1-6} alkylamino and C_{2-7} acylamino, or optionally substituted in two adjacent positions by methylene- or ethylene-dioxy; provided that R^4 cannot be a 3-alkyl-4-hydroxyphenyl or a 3,5-dialkyl-4-hydroxyphenyl group.

- 20 2. Compound as claimed in Claim 1, wherein R^4 is cyclohexyl, furyl, thienyl, pyridyl, pyrazinyl, or a phenyl group optionally substituted in any available position by one or two radicals selected from halogen, nitro, amino, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, pentafluoroethyl and C_{1-4} -monohaloalkyl or optionally substituted in two adjacent positions by methylene- or ethylene-dioxy, R^1 and R^2 are independently hydrogen, methyl or ethyl, and R^3 is:

- 25 (i) the group $-COOR^5$, where R^5 is C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl or di- C_{1-4} alkylamino- C_{1-4} alkyl; or
30 (ii) the group $-CO-R^6$ where R^6 is $-NHOH$ or $-NR^7R^8$ where R^7 and R^8 are independently hydrogen or C_{1-4} alkyl; or
(iii) the group $-CH_2OR^9$ where R^9 is hydrogen or C_{1-4} alkyl; or
(iv) the group $-COOH$ or an alkali or alkaline earth metal, aluminium or ammonium salt thereof; or
35 (v) a nitrile group.

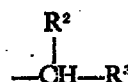
3. Compound as claimed in Claim 1, wherein R^1 , R^2 and R^3 are as defined in Claim 1, and R^4 is cyclohexyl, or a heteroaryl or phenyl group optionally substituted in any available position by one or more radicals selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-6} haloalkyl, nitro, amino, C_{1-6} alkylamino, and C_{2-7} acylamino or optionally substituted in two adjacent positions by methylene- or ethylene-dioxy.

- 40 4. Compound as claimed in Claim 2, having the formula:



II

wherein the group



- 45 is in the 5- or 6-position of the benzoxazole nucleus, R^4 is a phenyl group optionally substituted by one or two radicals selected from halogen, trifluoromethyl, methyl, methoxy, and nitro, R^2 is hydrogen or methyl and R^3 is as defined in parts (i) to (iv) in Claim 2.

5. Compound as claimed in Claim 3, wherein R^1 is hydrogen, R^2 is methyl, R^3 is as defined in parts (i) to (iv) in Claim 2, and R^4 is a phenyl group optionally sub-



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EXAMPLE 27

Suppositories each containing 250 mg of medicament are made as follows:—

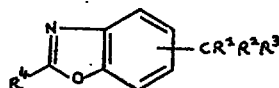
Medicament
Theobroma Oil

250 mg
to 2000 mg

- 5 The medicament is passed through a No. 60 mesh B.S.S. sieve and suspended in the theobroma oil, previously melted using the minimum of heat necessary. The mixture is then poured into a suppository mould of nominal 2 g capacity and allowed to cool.

WHAT WE CLAIM IS:—

10. 1. Compound of the formula:



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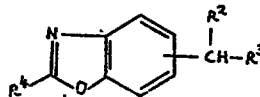
- 15 wherein the group $-CR^1R^2R^3$ is in the 5- or 6-position of the benzoxazole nucleus, R^1 and R^2 are independently hydrogen or C_{1-6} alkyl, R^3 is a nitrile group, carboxy or a salt, ester, amide or hydroxamic acid derivative thereof, or hydroxymethyl or an ester derivative thereof, and R^4 is cyclohexyl, or a heteroaryl or phenyl group optionally substituted in any available position by one or more radicals selected from C_{1-6} alkylsulphonyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, nitro, C_{2-7} acyl, hydroxy, amino, C_{1-6} alkylamino and C_{2-7} acylamino, or optionally substituted in two adjacent positions by methylene- or ethylene-dioxy; provided that R^4 cannot be a 3-alkyl-4-hydroxyphenyl or a 3,5-dialkyl-4-hydroxyphenyl group.

- 20 2. Compound as claimed in Claim 1, wherein R^4 is cyclohexyl, furyl, thienyl, pyridyl, pyrazinyl, or a phenyl group optionally substituted in any available position by one or two radicals selected from halogen, nitro, amino, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, pentafluoroethyl and C_{1-4} -monohaloalkyl or optionally substituted in two adjacent positions by methylene- or ethylene-dioxy, R^1 and R^2 are independently hydrogen, methyl or ethyl, and R^3 is:

- 25 (i) the group $-COOR^5$, where R^5 is C_{1-4} alkyl, amino- C_{1-4} alkyl, C_{1-4} alkylamino- C_{1-4} alkyl or di- C_{1-4} alkylamino- C_{1-4} alkyl; or
30 (ii) the group $-CO-R^6$ where R^6 is $-NHOH$ or $-NR^7R^8$ where R^7 and R^8 are independently hydrogen or C_{1-4} alkyl; or
(iii) the group $-CH_2OR^9$ where R^9 is hydrogen or C_{1-4} alkyl; or
(iv) the group $-COOH$ or an alkali or alkaline earth metal, aluminium or ammonium salt thereof; or
35 (v) a nitrile group.

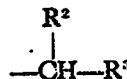
3. Compound as claimed in Claim 1, wherein R^1 , R^2 and R^3 are as defined in Claim 1, and R^4 is cyclohexyl, or a heteroaryl or phenyl group optionally substituted in any available position by one or more radicals selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, nitro, amino, C_{1-6} alkylamino, and C_{2-7} acylamino or optionally substituted in two adjacent positions by methylene- or ethylene-dioxy.

- 40 4. Compound as claimed in Claim 2, having the formula:



II

wherein the group



- 45 is in the 5- or 6-position of the benzoxazole nucleus, R^4 is a phenyl group optionally substituted by one or two radicals selected from halogen, trifluoromethyl, methyl, methoxy, and nitro, R^2 is hydrogen or methyl and R^3 is as defined in parts (i) to (iv) in Claim 2.

5. Compound as claimed in Claim 3, wherein R^1 is hydrogen, R^2 is methyl, R^3 is as defined in parts (i) to (iv) in Claim 2, and R^4 is a phenyl group optionally sub-



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stituted by one or two radicals selected from halogen, trifluoromethyl, methyl, methoxy and nitro.

6. Compound as claimed in Claim 3 or Claim 5, wherein R^3 is the group $-\text{COOR}^5$ in which R^5 is C_{1-4} alkyl or the group $-\text{COOH}$ or an alkali or alkaline earth metal, aluminium or ammonium salt thereof.

- | | | |
|----|---|----|
| 5 | 7. 2-(2-Phenyl-5-benzoxazolyl)propionitrile. | 5 |
| | 8. 2-(2-Phenyl-5-benzoxazolyl)propionic acid. | |
| | 9. 2-(2- <i>p</i> -Fluorophenyl-5-benzoxazolyl)propionic acid. | |
| | 10. 2-(2- <i>p</i> -Chlorophenyl-5-benzoxazolyl)propionic acid. | |
| 10 | 11. 2-(2- <i>m</i> -Chlorophenyl-5-benzoxazolyl)propionic acid. | 10 |
| | 12. 2-(2- <i>p</i> -Methylphenyl-5-benzoxazolyl)propionic acid. | |
| | 13. 2-(2- <i>m</i> -Methylphenyl-5-benzoxazolyl)propionic acid. | |
| 10 | 14. 2-(2- <i>o</i> -Methylphenyl-5-benzoxazolyl)propionic acid. | |
| | 15. 2-(2- <i>p</i> -Methoxyphenyl-5-benzoxazolyl)propionic acid. | |
| 15 | 16. 2-(2- <i>o</i> -Hydroxy- <i>p</i> -chlorophenyl-5-benzoxazolyl)propionic acid. | 15 |
| | 17. 2-(2- <i>o</i> -Hydroxy- <i>p</i> -chlorophenyl-5-benzoxazolyl)propionitrile. | |
| | 18. 2-(2- <i>p</i> -Chlorophenyl-5-benzoxazolyl)propionitrile. | |
| | 19. 2-(2- <i>p</i> -Acetylphenyl-5-benzoxazolyl)propionic acid. | |
| | 20. 2-(2- <i>p</i> -Bromophenyl-5-benzoxazolyl)propionic acid. | |
| 20 | 21. Ethyl 2-(2-phenyl-5-benzoxazolyl)propionate. | 20 |
| | 22. Ethyl 2-(2- <i>p</i> -chlorophenyl-5-benzoxazolyl)propionate. | |
| | 23. 2-(2-Phenyl-5-benzoxazolyl)propyl alcohol. | |
| 15 | 24. 2-Phenyl-5-benzoxazolylacetoneitrile. | |
| | 25. 2-Phenyl-5-benzoxazolylacetic acid. | |
| 25 | 26. 2-Phenyl-6-benzoxazolylacetic acid. | 25 |
| | 27. 2-Phenyl-6-benzoxazolylacetoneitrile. | |
| | 28. Ethyl 2-phenyl-6-benzoxazolylacetate. | |
| 20 | 29. Ethyl 2-(2-phenyl-6-benzoxazolyl)propionate. | |
| | 30. 2-(2-Phenyl-6-benzoxazolyl)propanol. | |
| 30 | 31. 2-(2-Phenyl-6-benzoxazolyl)propionamide. | 30 |
| | 32. 2-(2-Phenyl-5-benzoxazolyl)propionamide. | |
| | 33. 2-(2- <i>p</i> -Chlorophenyl-5-benzoxazolyl)propionamide. | |
| 25 | 34. 2-(2-Phenyl-6-benzoxazolyl)propionic acid. | |
| | 35. Ethyl 2-(2- <i>p</i> -chlorophenyl-6-benzoxazolyl)propionate. | |
| 35 | 36. 2-(2- <i>p</i> -Chlorophenyl-6-benzoxazolyl)propionic acid. | 35 |
| | 37. Ethyl 2-[2-(3,4-methylenedioxyphenyl)-5-benzoxazolyl]propionate. | |
| 30 | 38. 2-[2-(3,4-methylenedioxyphenyl)-5-benzoxazolyl]propionic acid. | |
| | 39. 2-[2-(3,4-dichlorophenyl)-5-benzoxazolyl]propionic acid. | |
| | 40. 2-[2-(2,4-dichlorophenyl)-5-benzoxazolyl]propionic acid. | |
| 40 | 41. Ethyl 2-(2- <i>p</i> -methylsulphonylphenyl-5-benzoxazolyl)propionate. | 40 |
| | 42. 2-[2-(2-Furyl)-5-benzoxazolyl]propionic acid. | |
| | 43. 2-(2-Cyclohexyl-5-benzoxazolyl)propionic acid. | |
| 35 | 44. 2-(2- <i>m</i> -Trifluoromethylphenyl-5-benzoxazolyl)propionic acid. | |
| | 45. 2-[2-(2-Thienyl)-5-benzoxazolyl]propionic acid. | |
| 45 | 46. 2-(2- <i>o</i> -Chlorophenyl-5-benzoxazolyl)propionic acid. | 45 |
| | 47. 2-(2- <i>p</i> -Trifluoromethylphenyl-5-benzoxazolyl)propionic acid. | |
| | 48. 2-(2- <i>p</i> -Iodophenyl-5-benzoxazolyl)propionic acid. | |
| 40 | 49. 2-(2- <i>m</i> -Fluorophenyl-5-benzoxazolyl)propionic acid. | |
| | 50. 2-[2-(3,5-Dichlorophenyl)-5-benzoxazolyl]propionic acid. | |
| 50 | 51. 2-(2- <i>o</i> -Fluorophenyl-5-benzoxazolyl)propionic acid. | 50 |
| | 52. 2-(2- <i>p</i> -Fluorophenyl-6-benzoxazolyl)propionic acid. | |
| | 53. 2-(2- <i>o</i> -Chlorophenyl-6-benzoxazolyl)propionic acid. | |
| | 54. Ethyl 2-(2- <i>o</i> -Chlorophenyl-6-benzoxazolyl)propionate. | |
| 55 | 55. 2-[2-(3-Pyridyl)-5-benzoxazolyl]propionic acid. | |
| | 56. 2-[2-(4-Pyridyl)-5-benzoxazolyl]propionic acid. | |
| | 57. 2-[2-(2-Pyridyl)-5-benzoxazolyl]propionic acid. | |
| | 58. <i>N,N</i> -Diethyl-2-(2-phenyl-5-benzoxazolyl)propionamide. | |
| | 59. 2-(2-Phenyl-5-benzoxazolyl)propionylhydroxamic acid. | |
| 60 | 60. 2-(<i>p</i> -Chlorophenyl)-5-benzoxazolylacetic acid. | 60 |
| | 61. 2-(2-Phenyl-5-benzoxazolyl)isobutyric acid. | |
| | 62. 2-[2-(3-Nitro-4-chlorophenyl)-5-benzoxazolyl]propionic acid. | |
| | 63. 2-(2- <i>p</i> -Nitrophenyl-5-benzoxazolyl)propionic acid. | |
| | 64. 2-(2-Phenyl-6-benzoxazolyl)ethanol. | |
| 65 | 65. Alkali metal salts and C_{1-4} alkyl esters of the acids claimed in any one of Claims 8 to 16, 19, 20, 25, 26, 34, 36, 38, to 40, 42, to 53, 55, to 57, 60 and 61 to 63. | 65 |

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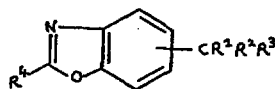
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66. Pharmaceutical composition comprising a pharmacologically active compound of the formula:



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wherein the group $-CR^1R^2R^3$ is in the 5- or 6-position of the benzoxazole nucleus, R^1 and R^2 are independently hydrogen or C_{1-6} alkyl, R^3 is carboxy or a salt, ester, amide or hydroxamic acid derivative thereof, or hydroxymethyl or an ester derivative thereof, and R^4 is cyclohexyl, or a heteroaryl or phenyl group optionally substituted in any available position by one or more radicals selected from C_{1-6} alkylsulphonyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, nitro, C_{2-7} acyl, hydroxy, amino, C_{1-6} alkylamino and C_{2-7} acylamino or optionally substituted in two adjacent positions by methylene- or ethylene-dioxy, in association with at least one pharmaceutically acceptable carrier therefor.

67. Composition as claimed in Claim 66, wherein R^4 in said active compound of formula I is cyclohexyl, or a heteroaryl or phenyl group optionally substituted in any available position by one or more radicals selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, nitro, hydroxy, amino, C_{1-6} alkylamino and C_{2-7} acylamino or optionally substituted in two adjacent positions by methylene- or ethylene-dioxy.

68. Composition as claimed in Claim 66, wherein said active compound is a compound as claimed in Claim 4.

69. Composition as claimed in Claim 67, wherein said active compound is a compound as claimed in Claim 5 or Claim 6.

70. Composition as claimed in Claim 67 or Claim 69, wherein said active compound is a compound as claimed in any one of Claims 8 to 16, 20 to 23, 25, 26, 28 to 40, and 42 to 65.

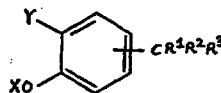
71. Composition as claimed in Claim 67, wherein said active compound is selected from:

- (a) 2-(2-*p*-chlorophenyl-6-benzoxazolyl)propionic acid;
- (b) 2-(2-*p*-chlorophenyl-5-benzoxazolyl)propionic acid;
- (c) 2-(2-*o*-chlorophenyl-5-benzoxazolyl)propionic acid;
- (d) 2-[2-(2,4-dichlorophenyl)-5-benzoxazolyl]propionic acid;
- (e) 2-(2-*p*-fluorophenyl-5-benzoxazolyl)propionic acid;
- (f) 2-(2-*p*-bromophenyl-5-benzoxazolyl)propionic acid;
- (g) 2-(2-phenyl-5-benzoxazolyl)propionic acid;
- (h) 2-(2-*p*-iodophenyl-5-benzoxazolyl)propionic acid;
- (i) alkali metal salts of compounds (a) to (h) above; and
- (j) C_{1-4} alkyl esters of compounds (a) to (h) above.

72. Composition as claimed in any one of Claims 66 to 71, in dosage unit form containing from 25 to 500 mg. of said active compound.

73. Pharmaceutical composition substantially as described in any one of Examples 24 to 27.

74. Process for preparing a compound of the formula I as claimed in claim 1, which process comprises cyclising a compound of the formula:



III

wherein either X is hydrogen or the group R^4CO- and Y is H_2N- , or X is hydrogen and Y is the group $R^4CO-NH-$ or $R^4CH=N-$, the cyclisation being carried out, in the case where X is hydrogen and Y is H_2N- , in the presence of a cyclising agent capable of donating the required group R^4 .

75. Process as claimed in Claim 74, wherein R^4 is cyclohexyl, furyl, thienyl, pyridyl, pyrazinyl, or a phenyl group optionally substituted in any available position by one or two radicals selected from halogen, nitro, amino, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, pentafluoroethyl and C_{1-4} -monohaloalkyl or optionally substituted in two adjacent positions by methylene- or ethylene-dioxy, R^1 and R^2 are independently hydrogen, methyl or ethyl, and R^3 is:

- (i) the group $-COOR^5$, where R^5 is C_{1-4} alkyl, amino- C_{1-4} alkyl; C_{1-4} alkyl-amino, C_{1-4} alkyl or di- C_{1-4} alkylamino- C_{1-4} alkyl; or
- (ii) the group $-CO-R^6$ where R^6 is $-NHOH$ or $-NR^7R^8$ where R^7 and R^8 are independently hydrogen or C_{1-4} alkyl; or



28 (29)

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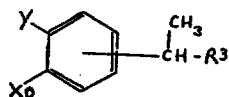
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- (iii) the group $-\text{CH}_2\text{OR}^3$ where R^3 is hydrogen or C_{1-6} alkyl;
 (iv) the group $-\text{COOH}$ or an alkali or alkaline earth metal, aluminium or ammonium salt thereof; or
 (v) a nitrile group.

5 76. Process as claimed in Claim 74, wherein R^1 , R^2 and R^3 are as defined in Claim 74, and R^4 is cyclohexyl, or a heteroaryl or phenyl group optionally substituted in any available position by one or more radicals selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, nitro, amino, C_{1-6} alkylamino and C_{2-7} acylamino or optionally substituted in two adjacent positions by methylene- or ethylene-dioxy.

10 77. Process as claimed in Claim 74 for preparing a compound of formula I in which R^1 is hydrogen, R^2 is methyl, R^3 is as defined in parts (i) to (iv) in Claim 75, and R^4 is a phenyl group optionally substituted by one or two radicals selected from halogen, trifluoromethyl, methyl, methoxy, nitro or hydroxy, which process comprises cyclising a compound of the formula:



15 wherein either X is hydrogen or the group $\text{R}^4\text{CO}-$ and Y is $\text{H}_2\text{N}-$, or X is hydrogen and Y is the group $\text{R}^4\text{CO}-\text{NH}-$ or $\text{R}^4\text{CH}=\text{N}-$, the cyclisation being carried out, in the case where X is hydrogen and Y is $\text{H}_2\text{N}-$, in the presence of a cyclising agent capable of donating the required group R^4 .

20 78. Process as claimed in Claim 74, wherein said cyclising agent is a compound of formula R^4COOH , $(\text{R}^4\text{CO})_2\text{O}$, R^4COCl , R^4CONH_2 , $\text{R}^4\text{CONHNH}_2$, R^4CN , $\text{R}^4\text{C(OR')}=\text{NH}$ or $\text{R}^4\text{CCl}=\text{NR}'$ where R' is C_{1-6} alkyl and R^4 is as defined in Claim 74.

25 79. Process of preparing a compound of formula I as claimed in claim 1 wherein a different compound of formula I is subjected to one or more of the following reactions:

- (a) where R^3 is a nitrile group, reaction with an appropriate alcohol under acidic conditions to produce the corresponding compound of formula I in which R^3 is an esterified carboxy group;
 (b) when R^3 is a nitrile group, hydrolysis to the corresponding compound of formula I in which R^3 is a carboxy group;
 (c) when R^3 is an esterified carboxy group, reaction with hydroxylamine to produce the corresponding hydroxamic acid derivative of formula I;
 (d) when R^3 is carboxy or esterified carboxy, reduction to the corresponding compound of formula I in which R^3 is hydroxymethyl;
 (e) when R^3 is hydroxymethyl, conversion to a corresponding esterified alcohol by reaction with an appropriate acid;
 (f) when R^3 is carboxy, conversion to a salt by reaction with an appropriate base and *vice versa* by treatment with an acid;
 (g) when R^3 is carboxy or salified carboxy, esterification by treatment with an appropriate alcohol or by treatment with a halide of the ester moiety or a salt of that halide if the ester moiety contains a basic nitrogen atom;
 (h) when R^3 is an esterified carboxy group, hydrolysis to the corresponding compound of formula I in which R^3 is carboxy or hydroxymethyl;
 (i) when R^3 is carboxy or an esterified carboxy group, reaction with ammonia or a primary or secondary amine to produce a corresponding amide of formula I;
 (j) when R^1 and/or R^2 is hydrogen, alkylation to the corresponding compound in which R^1 and/or R^2 is C_{1-6} alkyl.

50 80. Process for preparing a benzoxazole derivative as claimed in claim 1, substantially as hereinbefore described in any one of Examples 1 to 23.

81. Benzoxazole derivatives, whenever prepared by the process claimed in any one of Claims 74 to 80.

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