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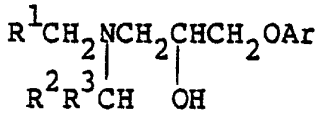
(54) Title: STEREOSELECTIVE PROCESS AND CHIRAL INTERMEDIATES FOR ARYLOXYDROPANOLAMINES



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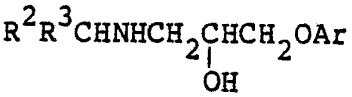

(VII)

(57) Abstract

The S-isomer of a compound of the formula (V), wherein Ar is an optionally substituted aryl, heteroaryl or heterocyclic group, and R^1 is phenyl optionally substituted by C_{1-6}alkoxy or C_{1-6}alkyl and its use in a process for the preparation of the S-isomer of compounds of formula (VII), wherein the group R^2R^3CH- is optionally substituted alkyl.

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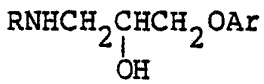
Stereoselective process and chiral intermediates for Aryloxydropanolamines.

The present invention relates to a general method for preparing chiral ß-adrenoceptor antagonists and to intermediates therefor. ß-Adrenoceptor antagonists are useful in the treatment of a range of diseases for example hypertension, angina, myocardial infarction, arrhythmias, thyrotoxicosis, anxiety, migraine, tremor, glaucoma and congestive heart failure.

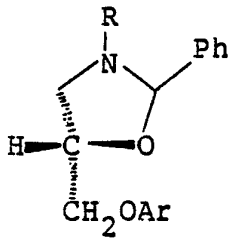
Many ß-adrenoceptor antagonists have the general formula (I):-



(I)

wherein Ar is an optionally substituted aryl, heteroaryl or heterocyclic group as known in the art, and R is an optionally substituted alkyl group as known in the art for example a group R^2R^3CH- as hereinafter defined. The carbon atom bearing the hydroxy group is chiral and it is generally acknowledged that ß-adrenoceptor activity resides in the S-isomer. Generally such S-isomers are prepared by resolution or by asymmetric synthesis. However, these processes are difficult and inefficient and, in general, S-isomers of ß-adrenoceptor antagonists substantially free of the corresponding R-isomer have not been widely commercialised.

In an asymmetric synthesis known in the art (GB 2130585 A) a compound of the formula (II):



(II)

wherein R and Ar are as hereinbefore defined, is treated with to form the compound of the formula (I). This intermediate compound of the formula (II) is derived from the appropriate isomer of a compound of the formula (III):

$$RNHCH_2CH(OH)CH_2OH \qquad (III)$$

wherein R is as hereinbefore defined, by reaction with benzaldehyde and modification of the terminal hydroxy group to introduce the -O-Ar group.

A wide variety of groups R are known in the ß-adrenoceptor antagonist art. Clearly the group R is introduced at a very early stage of the overall asymmetric synthesis. Therefore it is particularly inefficient to synthesise chiral compounds as this necessitates a complete synthetic sequence for each value of R.

It is particularly beneficial to have a general intermediate that can provide a wide range of chiral ß-adrenoceptor antagonists with introduction of the group R at a late stage of the synthetic sequence. The present invention provides such an intermediate, additionally this is readily formed in good yields.

Accordingly, the present invention provides the S-isomer of a compound of the formula (IV):

$$R^1CH_2NHCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2OAr \qquad (IV)$$

wherein Ar is an optionally substituted aryl, heteroaryl

or heterocyclic group, and R^1 is phenyl optionally substituted by C_{1-6}alkoxy or C_{1-6}alkyl.

In this specification 'S-isomer' relates to the absolute configuration of the pictured carbon atom bearing the hydroxy group; and is preferably provided substantially free of the corresponding R-isomer.

Suitably Ar is an optionally substituted aryl, heteroaryl or heterocyclic group as known in the ß-adrenoceptor antagonist art.

More suitably Ar is phenyl optionally substituted by one, two or three groups selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{2-6}alkenyl, C_{2-6}alkenyloxy, C_{3-10}cycloalkyl, halo, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkylcarbamoyl, arylcarbamoyl, arylC_{1-6}alkyl, arylC_{1-6}alkoxy, C_{1-6}alkanoylamino, arylC_{1-6}alkanoylamino, arylC_{1-6}alkanoyl, arylC_{2-6}alkenyl, carbamoylC_{1-6}alkyl, C_{1-6}alkylcarbamoyl-C_{1-6}alkyl, di-C_{1-6}alkylcarbamoylC_{1-6}alkyl, aryl, aryloxy, C_{1-6}alkylthio, cyano, hydroxyC_{1-6}alkyl, C_{1-6}alkanoyl-C_{1-6}alkyl, amino, C_{1-6}alkylamino, di-C_{1-6}alkylamino, morpholino, C_{3-10}cycloalkylC_{1-6}alkoxy, C_{3-10}cycloalkylC_{1-6}alkoxyC_{1-6}alkyl, C_{3-10}cycloalkylC_{1-6}alkoxy-C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, C_{3-10}cycloalkylC_{1-6}alkyl, ureido, C_{1-6}alkylureido, C_{1-6}alkylsulphonamido and arylsulphonamido. Suitably also Ar is indanyl, indenyl, naphthyl, 5-oxotetrahydronaphthyl, 6-oxotetrahydronaphthyl, tetrahydronaphthyl, 5,8-dihydronaphthyl or 7,8-dihydroxytetrahydronaphthyl.

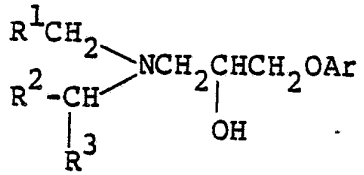
When Ar is an optionally substituted heteroaryl or heterocyclic group suitably it contains up to three heteroatoms selected from oxygen, sulphur and nitrogen. For example, pyridinyl, pyrimidinyl, quinolinyl, indolyl, and 1,2,5-thiadiazol-3-yl. Suitable substituents, where appropriate, are those described hereinabove as suitable for substitution on phenyl.

Examples of groups Ar are 2-cyanophenyl, 2-methylphenyl, 2,3-dimethylphenyl, 4-(2-methoxyethyl)phenyl, 4-(carbamoylmethyl)phenyl, 2-allyloxy, 4-butyronamidophenyl, 2-chlorophenyl, 2-methoxyphenyl, 2-morpholinophenyl, 4-(2-(cyclopropylmethoxy)ethyl)phenyl, 4-methanesulphonamidophenyl, 4-(2-acetylethyl)phenyl, 4-morpholino-1,2,5-thiadiazol-3-yl, 4-acetamidophenyl and phenyl.

Suitably R^1 is phenyl or phenyl substituted by one, two or three groups selected from C_{1-6}alkoxy and C_{1-6}alkyl, for example methylphenyl, methoxyphenyl and ethoxyphenyl. Preferably R^1 is phenyl.

The compounds of the formula (IV) are useful in that they can be converted to the S-isomers of a wide range of ß-adrenoceptor antagonists in two steps.

Accordingly in another aspect the present invention provides a process for preparing the S-isomer of a compound of the formula (V):



(V)

where R^1 and Ar are as hereinbefore defined, and R^2R^3CH- represents optionally substituted alkyl: which process comprises reacting the S-isomer of a

compound of the formula (IV) as hereinbefore defined with a compound of the formula (VI), or a compound of the formula (VIA) under conditions of reductive alkylation:

R^2R^3CH-X (VI) $R^2R^3C=O$ (VIA)

wherein R^2 and R^3 are as hereinbefore defined and X is a displaceable group.

In a further aspect the present invention provides the S-isomer of a compound of the formula (V). Suitable and preferred values for R^1 and Ar are as described for compounds of the formula (IV).

Suitably R^2R^3CH- is a moiety known in the ß-adrenoceptor antagonist art, for example R^2 is hydrogen or C_{1-6}alkyl, preferably hydrogen or methyl, and R^3 is optionally substituted C_{1-6}alkyl. Suitable substituents for R^3 include those of the following sub-formulae:

i) $R^a-O-C(=O)-$

ii) $R^a-CO-NH-$

iii) R^a-NR^b-CO-

iv) $R^a-NR^b-CO-NH-$

wherein R^a is C_{1-6}alkyl, phenyl or phenylC_{1-6}alkyl, said phenyl groups being optionally substituted by one, two or three groups as defined hereinabove with reference to suitable substituents for Ar; and R^b is hydrogen or C_{1-6}alkyl. Preferably R^2R^3CH- is isopropyl.

The reaction between compounds of the formulae (IV) and (VI) is performed in conventional manner. Suitably X is halo, for example chloro or bromo. Conveniently the reaction is performed in a substantially inert solvent.

The reaction between compounds of the formulae (IV) and (VIA) is performed under conventional reductive alkylation conditions, for example in a substantially inert solvent in the presence of Raney nickel.

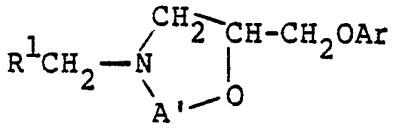
In another aspect the present invention provides a process for the preparation of the S-isomer of a compound of the formula (VII):

$$R^2R^3CHNHCH_2\underset{\underset{OH}{|}}{CH}CH_2OAr \qquad (VII)$$

wherein R^2, R^3 and Ar are as hereinbefore defined, which comprises reducing the S-isomer of a compound of the formula (V) as hereinbefore defined.

Suitably the reduction is performed using catalytic hydrogenation in conventional manner. For example using conventional transition metal catalysts such as palladium on a suitable carrier with hydrogen gas or under conditions of catalytic transfer hydrogenation. For example palladium on carbon and palladium hydroxide on carbon may be used. Hydrogenation with hydrogen gas may be performed at non-extreme pressure for example between atmospheric pressure and pressures of 10 atmospheres. Suitably hydrogenation is performed in a C_{1-4}alkanol for example ethanol. Catalytic transfer hydrogenation can be effected for example using hydrazine.

The S-isomers of the compounds of the formula (IV) as hereinbefore defined can be prepared by reacting the S-isomer of a compound of the formula (VIII) with acid:

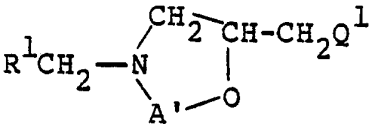


(VIII)

wherein R^1 and Ar are as hereinbefore defined, and A' is an acid-cleavable optionally substituted methylene protecting group for the N- and O- atoms.

Suitably A' is $>C=O$ or a group $-C(R^4)(R^5)-$ wherein R^4 and R^5 are independently C_{1-6}alkyl, for example they are both methyl. Suitably also A' is optionally substituted -CH(Ph)-, preferably A' is -CH(Ph)-. Suitably such a reaction is performed in an aqueous or mixed aqueous solvent system. Conveniently concentrated hydrochloric acid is used.

The S-isomers of the compounds of the formula (VIII) are conveniently prepared from the S-isomer of a compound of the formula (IX):



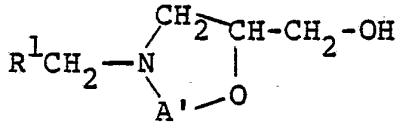
(IX)

wherein A' and R^1 are as hereinbefore defined and Q^1 is a displaceable group, and an anion of the formula ^-OAr wherein Ar is as hereinbefore defined.

In the compounds of the formula (IX) suitably Q^1 is a sulphonate such as a C_{1-6}alkanesulphonate for example methanesulphonate, trifluoromethanesulphonate or an arylsulphonate for example benzenesulphonate or toluene-p-sulphonate, or a phosphonate or phosphinate for example diphenylphosphonate or diphenylphosphinate, or Q^1 is halo for example bromo or chloro. The anion of the formula ^-OAr is conveniently formed in situ from the

corresponding hydroxy compound. The anion of the formula ^{-}OAr is conveniently generated by the action of base, for example an alkali metal hydroxide or alkaline earth metal hydroxide, for example sodium hydroxide, or for example an organic base such as triethylamine. In a suitable alternative the anion of the formula ^{-}OAr is introduced into the reaction as the alkali metal salt of the hydroxy compound, for example the sodium or potassium salt. The reaction between the compound of the formula (IX) and an anion of the formula ^{-}OAr is conveniently performed in a substantially inert aprotic solvent such as dimethylformamide.

The S-isomers of the compounds of the formula (IX) can be prepared by reacting the S-isomer of a compound of the formula (X) with a compound capable of introducing the group Q^1 :



(X)

wherein R^1 and A' are as hereinbefore defined.

Suitable reagents for introducing the group Q^1 are sulphonylating agents for example methanesulphonyl chloride, benzenesulphonyl chloride and toluene-p-sulphonyl chloride; phosphoryl and phosphinyl reagents for example diphenylphosphoryl chloride and diphenylphosphinyl chloride; and halogenating agents for example thionyl chloride or thionyl bromide, used in conventional manner.

The S-isomers of the compounds of the formula (X) can be prepared in conventional manner by reacting an appropriate precursor, for example a ketone or optionally substituted benzaldehyde, with the S-isomer of a compound

of the formula (XI):

$$R^1CH_2NHCH_2\underset{\underset{OH}{|}}{CH}CH_2OH \qquad (XI)$$

wherein R^1 is as hereinbefore defined.

The S-isomers of the compounds of the formula (XI) represent another important intermediate and are a further aspect of the invention. Preferably in such compounds R^1 is phenyl.

The S-isomers of the compounds of the formula (XI) can be prepared by reacting the S-isomer of a compound of the formula: $CHOCH(OH)CH_2OH$ with a compound of the formula: $R^1CH_2NH_2$ wherein R^1 is as hereinbefore defined, in the presence of a reducing agent, for example hydrogen and a transition metal catalyst.

The following Examples illustrate the invention.

Example 1

To a stirred suspension of mannitol diacetonide (26.2 g) in benzene (800 ml) was added lead tetraacetate (44.2 g) over 5 minutes. The resultant solid was broken up to give a cloudy solution, stirred for 45 minutes, filtered, evaporated under reduced pressure and distilled to give as an oil, acetone-d-glyceraldehyde (17.7 g), b.p. 44-8°C/11 mm Hg. To a solution of this in methanol (60 ml), at 5°C, was added slowly a solution of benzylamine (10.7 g) in methanol (60 ml). This mixture was added to a slurry of 5% palladium on carbon (1.5 g) in methanol (40 ml) and hydrogenated at 344 KPa (50 p.s.i.) for 30 minutes. The mixture was filtered, treated with 6N hydrochloric acid (150 ml), distilled until the vapour

temperature was 98°C and heated under reflux for one hour. The mixture was cooled, taken to pH 14 with sodium hydroxide, extracted into dichloromethane (3 times), dried and evaporated under reduced pressure to give an oil. This oil was extracted with boiling ether (twice), filtered whilst warm and on standing gave as a crystalline solid (S)-(-)-3-benzylamino-1,2-propanediol (10.1 g), $[\alpha]_D^{25}$ = -25.72° [concentration 1.01% in ethanol : water: concentrated HCl (17:2:1)], m.p. 63°C.

Example 2

Part of the product from Example 1 (7.24 g) in warm toluene (35 ml) and benzaldehyde (4.66 g) were stirred at room temperature for 90 minutes, then stirred under reflux for 60 minutes removing water using a Dean-Stark apparatus. The solution was then cooled, evaporated under reduced pressure to give an oil which was crystallised from ethyl acetate to give (S)-(-)-2-phenyl-3-benzyl-5-hydroxymethyl-oxazolidine (8.1 g), m.p. 100°C.

Example 3

Part of the product from Example 2 (6.73 g) in pyridine (10 ml) and toluene-p-sulphonyl chloride (4.8 g) were stirred at room temperature for 2 hours (initial cooling). Potassium carbonate (4.13 g) in water (20 ml) was added cautiously and the product extracted into dichloromethane (3 times). The organic extracts were dried and evaporated under reduced pressure to give the tosylate (10.7 g) as an oil. The tosylate in dimethylformamide (12.5 ml) was added in portions to a solution of the anion of 4-(2-(cyclopropylmethoxy)ethyl)-phenol (4.8 g) (formed from sodium hydride (50% dispersion; 1.25 g)) in dimethylformamide (12.5 ml). The reaction mixture was heated at 70°C for 6 hours, poured on to ice

(90 g) and extracted into ether (3 times). The ether extracts were washed with water, dried and evaporated to give (S)-(-)-2-phenyl-3-benzyl-5-(4-(2-cyclopropylmethylmethoxy)ethyl)phenoxymethyl)oxazolidine as an orange oil (9.78 g).

Example 4

The oxazolidine from Example 3 (9.78 g) was slurried in a mixture of water (80 ml) and concentrated hydrochloric acid (20 ml) for one hour until the orange oil had changed to a pale yellow solid. The solid was filtered, washed with water, slurried with ether, filtered and dried under vacuum to give (S)-(-)-2-hydroxy-3-[4-(2-(cyclopropylmethoxy)ethyl)phenoxy]-N-benzylpropylamine as a hydrochloride (5.18 g), m.p. 172°C (recrystallisation from acetonitrile), $[\alpha]_D^{25}$ = -14.0° [concentration 1.11% in ethanol : water: concentrated HCl (17:2:1)], m.p. 172°C.

Example 5

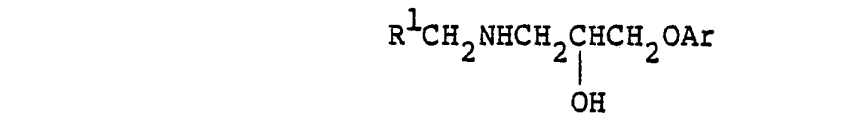
S-(-)-2-Hydroxy-3-[4-(2-(cyclopropylmethoxy)ethyl)-phenoxy]-N-benzylpropylamine (1.77 g) and isopropyl iodide (0.98 g) were heated under reflux in ethanol (20 ml) for 12 hours. Ethanol was removed under reduced pressure, the resultant oil dissolved in dichloromethane (20 ml), washed with base (NaOH solution, pH 14, 20 ml), separated, dried ($MgSO_4$), filtered and evaporated to give a pale brown oil. Column chromatography (silica gel:methanol: dichloromethane 1:9) gave S-(-)-2-hydroxy-3-[4-(2-(cyclopropylmethoxy)ethyl)phenoxy]-N-benzyl-N'-isopropylpropylamine as a pale oil (120 mg); ($CDCl_3$) 7.30 (5H,m, $\underline{Ph}CH_2N$), 3.90 (2H,m,$Ph\underline{CH_2}N$), 3.60 (2H,m,$CH(OH)-\underline{CH_2}O-$), 2.98 (1H,m,$NC\underline{H}(CH_3)_2$), 2.60 (2H,m,$N\underline{CH_2}CH(OH)$), 1.07 (3H,d,$NCH(\underline{CH_3})_2$), 1,01 (3H,d,$NH(\underline{CH_3})_2$), ppm.

Example 6

The product from Example 5 (100 mg) was dissolved in ethanol (10 ml), in the presence of palladium hydroxide on carbon and the mixture hydrogenated at 344 KPa (50 p.s.i.) for 3 hours. Filtration to remove catalyst followed by evaporation of solvent gave a pale oil which was purified by preparative tlc (dichloromethane:methanol (saturated with ammonia) 9:1), to give S-(-)-2-hydroxy-3-[4-(2-(cyclopropylmethoxy)ethyl)phenoxy]-N-isopropylpropylamine, 28.5 mg, identical with an authentic sample by chromatography and a nuclear magnetic resonance spectrum.

Claims :

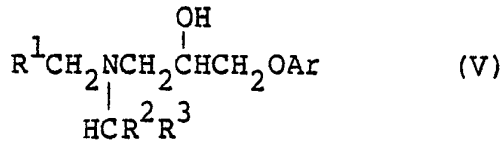
1. A compound of the formula:



(IV)

wherein R^1 is phenyl optionally substituted by C_{1-6}alkoxy or C_{1-6}alkyl, and Ar is an optionally substituted aryl, heteroaryl or heterocyclic group: in the form of the S-isomer.

2. A compound of the formula



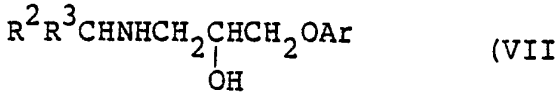
(V)

where R^1 is phenyl optionally substituted by C_{1-6}alkoxy or C_{1-6}alkyl, R^2R^3CH- is optionally substituted alkyl and Ar is an optionally substituted aryl, heteroaryl or heterocyclic group: in the form of the S-isomer.

3. A compound according to claim 1 or claim 2 wherein R^1 is phenyl.

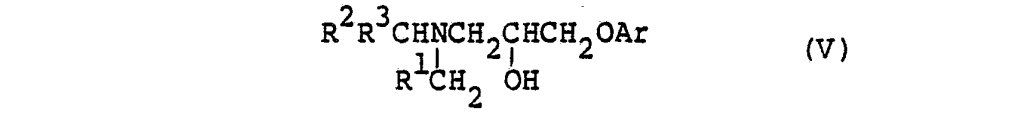
4. A compound according to claim 2 or 3 wherein R^2R^3CH- is isopropyl.

5. A process for preparing the S-isomer of a compound of the formula (VII):



(VII)

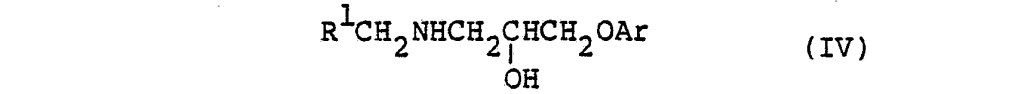
wherein R^2, R^3 and Ar are as defined in claim 1, which comprises reducing the S-isomer of a compound of the formula (V):



(V)

wherein R^2, R^3, Ar and R^1 are as defined in claim 2.

6. A process for preparing the S-isomer of a compound of the formula (V) as defined in claim 2 which comprises reacting the S-isomer of a compound of the formula (IV):



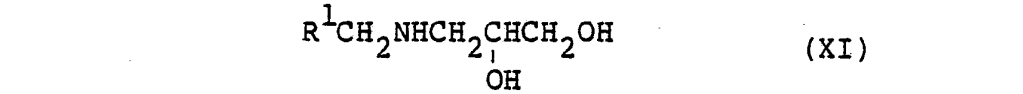
(IV)

wherein R^1 and Ar are as defined in claim 2, with a compound of the formula (VI), or with a compound of the formula (VIA) under conditions of reductive alkylation:

(VI) (VIA)

wherein R^2 and R^3 are as defined in claim 2 and X is a displaceable group.

7. A compound of the formula (XI):



(XI)

wherein R^1 is as defined in claim 1: in the form of the S-isomer.

8. A compound according to claim 7 wherein R^1 is phenyl.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 85/00514

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 C 93/00; C 07 C 91/10

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 C 93/00 C 07 C 91/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	GB, A, 1591723 (CIBA-GEIGY AG) 24 June 1981, see pages 13,14; example 6	5,6
Y	US, A, 4210653 (J.J. BALDWIN) 1 July 1980, see column 4, line 42 - column 5, line 64; column 6, lines 3-16	5,6

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12th February 1986	06 MARS 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 85/00514 (SA 11275)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 19/02/86

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A- 1591723	24/06/81	NL-A-	7710394	07/04/78
		BE-A-	858867	20/03/78
		FR-A,B	2367065	05/05/78
		DE-A-	2740678	06/04/78
		CH-A-	607585	15/09/78
		JP-A-	53050177	08/05/78
		AU-A-	2912577	05/04/79
		AT-B-	358037	11/08/80
		AT-B-	358042	11/08/80
		AT-B-	358586	25/09/80
		AT-B-	360021	10/12/80
		CA-A-	1105021	14/07/81
		AU-B-	514676	19/02/81
		SE-A-	7710250	06/04/78
US-A- 4210653	01/07/80	EP-A,B	0006614	09/01/80
		JP-A-	55007287	19/01/80
		US-A-	4336261	22/06/82
		AT-B-	E4707	15/10/83