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(54) Title: SUBSTITUTED BICYCLO (2,2,1) HEPTANES AND HEPT-2-ENES

(57) Abstract

Novel bicyclo (2,2,1) heptanes and hept-2Z-enes are substituted at the 5-position by a 6-carboxyhex-2-enyl group or a modification thereof, and at the 6-position by an aldoxime or ketoxime group which is O-substituted by an aliphatic hydrocarbon residue, an aromatic residue, or an aliphatic hydrocarbon residue substituted directly or through an oxygen or sulphur atom by an aromatic residue. Such compounds may be prepared by the action of an oximating agent on an intermediate which is substituted at the 6-position by an aldehydic or ketonic carbonyl group. The compounds are of value for use in pharmaceutical compositions particularly in the context of the inhibition of thromboxane activity.

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SUBSTITUTED BICYCLO (2,2,1)HEPTANES AND HEPT-2-ENES

This invention relates to biologically active compounds and in particular to certain novel compounds exhibiting activity at thromboxane receptor sites.

Thromboxane A_2 (TXA_2), which is derived from arachidonic acid via prostaglandin H_2 (PGH_2), is implicated in several potentially noxious actions on various body systems, including platelet aggregation, bronchoconstriction and pulmonary and systemic vasoconstriction. Thus TXA_2 may be involved in the normal sealing of blood vessels following injury but in addition may contribute to pathological intravascular clotting or thrombosis. Moreover, the constrictor actions of TXA_2 on bronchiolar, pulmonary vascular and systemic vascular smooth muscle may be important in the development of several anaphylactic conditions including bronchial asthma. There is also some evidence to implicate PGH_2 and TXA_2 in the genesis of inflammation.

It is an object of the present invention to provide compounds having activity at thromboxane receptor sites, and most especially to to provide compounds which are inhibitors of thromboxane activity and are therefore of interest in one or more areas of medical treatment including the treatment of thrombotic disorders, the treatment of anaphylactic disease states, and treatments utilising anit-inflammatory agents.

Accordingly the present invention comprises a compound being a bicyclo[2,2,1] heptane or hept-2Z-ene which is substituted at the 5-position by a 6-carboxyhex-2-enyl group or a modificataion thereof as defined herein, and at the 6-postion by an aldoxime or ketoxime group which is O-substituted by an aliphatic hydrocarbon residue, an aromatic residue or an aliphatic hydrocarbon residue substituted directly or through an oxygen or sulphur atom by an aromatic residue.

Certain of the compounds containing a modified 6-carboxyhex-2-enyl group act through the conversion of the modified group back to the unmodified group <u>in vivo</u>. In addition to such bioprecursors, the invention also extends in general to other pharmaceutically acceptable bioprecursors for the bicyclo [2,2,1] heptanes and hept-2Z-enes described above, such a bioprecursor being a compound having a structural formula different from the active compound but which upon administration is converted thereto <u>in vivo</u>.

Modifications of the 6-carboxyhex-2-enyl group which may be made in compounds according to the present invention are of two types. Firstly, there are modifications which involve alteration of the hex-2-enyl group by one, or where appropriate by a combination, of the following: (a) reduction of the double bond optionally accompanied by the replacement of a carbon atom at the 5, 6 or even 7 position relative to the C_1 of the carboxylic acid group by a sulphur or particularly an oxygen atom; (b) alteration of the position of the double bond, for example to the 4,5 position; and (c) shortening or lengthening of the carbon chain, particularly by one of two methylene groups and conveniently at the end of the chain adjacent to the carboxy group.

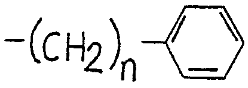
The second form of modification, which may if desired be combined with a modification of the first type, involves conversion of the carboxy group to a functional derivative including salts thereof. Functional derivatives described in the prostaglandin art are of particular interest, including esters such as alkyl esters, amides such as those containing the group $-CONHSO_2CH_3$ and variants thereon, and salts with various physiologically acceptable cations. Specific examples of salts are those with an alkali metal such as sodium or with quaternary ammonium ions or amines such as tris. As mentioned above, it will be appreciated that many of such compounds are in fact bioprecursors for the corresponding compound containing a carboxy group to which they are converted in vivo.

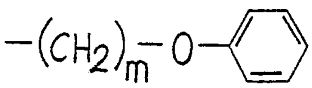
Ketoxime groups, -C(R)=NOR', in which R' is as defined above for the O-substituent, more usually contain organic groups R of the same general type as described for R^1, for example particularly aliphatic hydrocarbon or aromatic residues, or alternatively aliphatic hydrocarbon residues which are substituted, especially directly, but also through an oxygen or sulphur atom by an aromatic residue, specific examples being described later in relation to R'. Aldoxime groups, -CH=NOR', are however of particular interest.

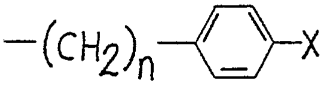
Aliphatic hydrocarbon residues constituting R' may conveniently be of one to five, six, seven, eight, nine, ten or even more carbon atoms, being for example a branched or unbranched alkyl group such as methyl, ehtyl, propyl, butyl,amyl, etc. Aromatic residues constituting R' are also of some interest and may be hydrocarbon or heterocyclic residues, which may be unsubstituted or substituted. The heterocyclic residues are more generally linked through a carbon atom so that residues such as pyrid-2-yl, pyrid-3-yl and pyrid-4-yl are of particular interest. Aromatic hydrocarbon residues such as phenyl are, however, of greater interest and these, and also the heterocyclic residues, may be substituted by one or more of various types of group, particularly by substituents being or containing a halogen residue (referred to hereinafter as 'a halogen substituent'), for example chloro and especially fluoro, and also halogen substituted alkyl groups such as CF_3, but also other substituents such as sulphonamide groups which may optionally be N-substituted, amino groups which may be free or substituted, for example dimethylamino, hydroxyl groups, methoxy and other higher alkoxy groups containing alkyl groups as described above, etc. Substitution may be present at one or more of the ortho, meta and para positions of a phenyl ring or at a combination of two or more such positions (including two similar positions), for example at the 2 and 4 positions. The position of substitution may have quite a significan effect upon the activity of a compound, particularly in the case of halogen substituents. Thus, for example, in the case of a phenoxyethyl O-substituted oxime, the order of interest in the positions of substitution is $o > m > p$ whilst in the case of a benzyl O-substituted oxime it is $o \sim p > m$, in view of the tendency, particularly with halogen substituent , for para substitution in the former case and meta substitution in the latter tend to lead to partial agonist activity as discussed hereinafter.

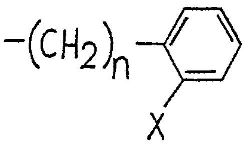
Of particular interest, however, are groups R' which are aliphatic hydrocarbon residues substituted directly or through a sulphur or particularly an oxygen atom by an aromatic residue. The aliphatic residues may be of a similar size to those described above but are preferably of three atoms, particularly of two atoms and especially of one atom, conveniently being branched or unbranched alkylene groups such as methylene, ethylene or propylene or corresponding trivalent groups of similar size. Similar aromatic hydrocarbon and heterocyclic residues are generally of interest for attachment to the aliphatic residues as have already been described above, the aromatic hydrocarbon residues again generally being of more interest than the heterocyclic residues. Heterocyclic residues, where used, are however of most interest when linked to the aliphatic hydrocarbon residue through the hetero atom such as in pyrid-1-yl. Substitution of an aliphatic hydrocarbon residue, particularly terminally, by two or even three aromatic aromatic residues and/or substitution through a sulphur or particularly an oxygen atom is of some considerable interest. In the latter instance, however, the aliphatic hydrocarbon residue is conveniently of at least two carbon atoms in view of the relative instability of the linkages $-O-CH_2-S-$ and $-O-CH_2-O-$.

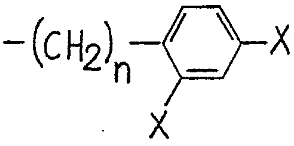
Examples of specific groups R' in ketoxime and aldoxime substituents -C(R)=NOR' and -CH=NOR' are:-

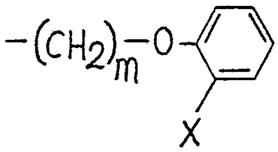


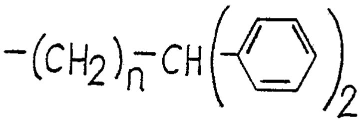


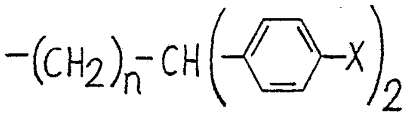


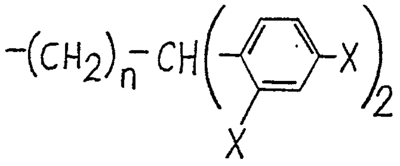




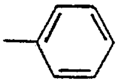






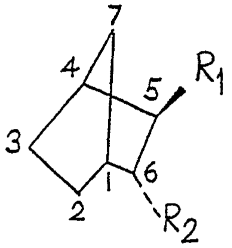


$-(CH_2)_p\ CH_3$

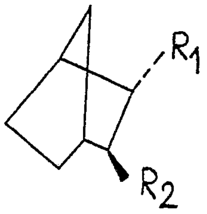


wherein n = 1, 2 or 3, m = 2 or 3, p = 1, 2, 3, 4, or 5, and X = Cl, F or CF_3.

It will be appreciated that the structures of the compounds described above provide various opportunities for the occurence of isomerism although the double bond of the unsaturated ring system is of the Z configuration. The substituents at the 5 and 6 positions of the ring may be in the *cis* or *trans* relationship to each other, compounds of the latter configuration being preferred. Moreover, as the ring system is further substituted by a divalent bridging group, then different isomers will exist which vary in which of the 5- and 6- substituents is disposed in a similar direction to the bridging group. Isomers of particular interest are (illustrated for the saturated ring system):

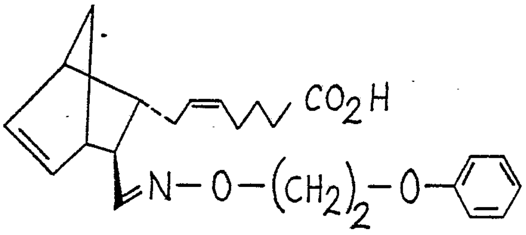


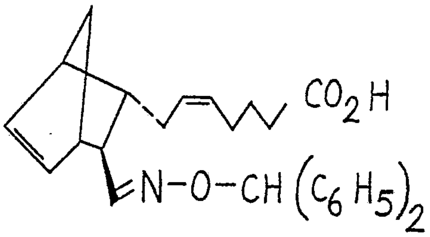
and, more particularly



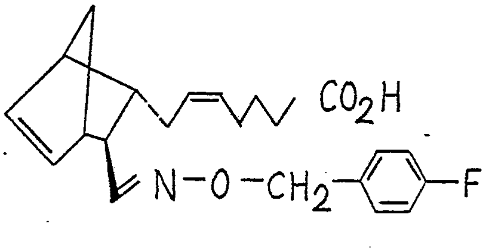
Where the first substituent is a 6-carboxyhex-2-enyl group or a group modified therefrom but still containing the double bond, then the configuration about this bond is preferably *cis* (Z) rather than *trans* (E). In the second substituent, although *syn* and *anti* isomerism is possible about $\rangle C{=}N$-double bond the isomers are often readily interconvertible at room temperature and exist as a mixture which shows biologically activity that may, however, derive predominantly from one isomer. In addition to the foregoing isomerism, the compounds of the present invention will generally be resolvable into enantiomeric forms and one among these may be preferred by virtue of biological activity or physical properties.

Examples of specific compounds according to the present invention are



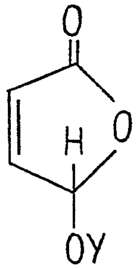


and



and its chloro and trifluoromethyl analogues, as well as the ring saturated analogues of these compounds.

Compounds according to the present invention may conveniently be prepared by using as a starting material a compound containing the unsaturated ring system and having substituents on the ring system which are suitable precursors for those in the final compound. The formation of such an unsaturated bicyclic ring system is conveniently effected by means of a Diels Alder reaction. Compounds containing the saturated ring systems are conveniently produced by reduction of the ring double bond, for example by the use of hydrogen in the presence of a catalyst such as palladium-charcoal, such reduction more usually being effected prior to modification of the substituents. A convenient starting material providing suitable precursors for the final substituents is a maleinaldehydic acid pseudo ester of formula



wherein Y represents a hydrocarbon residue, preferably an aliphatic residue such as methyl or especially ethyl. Following reaction of this compound with cyclopentadiene in a Diels Alder reaction, modification of the substituents provided by the ester is effected, conveniently to give initially a 6-carboxyhex-2-enyl group or a modification thereof and a formyl group, -CHO, which may readily be modified further as desired.

An example of such a procedure is shown on page 38 of this specification for the production of a bicyclo 2,2,1 hept-2Z-ene system (the numbering of the compounds corresponding to that used in Example 1 and which has also been followed in Example 2 for the ring saturated analogue. The following abbreviations are employed in the scheme: Ts, toluene sulphonyl; DMSO, dimethyl sulphoxide; Et, ethyl; Bu, butyl): The use of ethoxycarbonyl rather than methoxycarbonyl groups and of ethyl rather than methyl acetal groups has been found to be of value in this procedure. In the final stages of this procedure the acetal group of compound (7) is converted to a formyl group to give compound (8) or compound (8') and this formyl group is reacted with a suitable reagent or reagents to introduce the appropriate substituted oxime group, the carboxy group of the 6-carboxyhex-2-enyl group optionally being protected, thereby generally giving a slightly greater yield on oximation.

The introduction of the substituted oxime grouping may be effected by reaction of a suitable oximating agent either directly with the formyl group, in the case of aldoximes, or with the carbonyl group produced through the action of a Grignard reagent on the formyl group (and the subsequent oxidation of the secondary alcohol so formed, for example using Jones reagent) in the case of ketoximes. Such secondary alcohols, which are obtained in two isomeric forms owing to the presence of a new asymmetric centre therein, and also the ketones obtained therefrom, are included by the present invention in view of their value as intermediates in the preparation of the O-substituted ketoximes.

The oximating agent reacted with the -formyl or -C(R)=O group may conveniently take the form of a substituted hydroxylamine, NH_2-O-R'. Such a reaction is generally effected in the presence of a base, for example pyridine. As indicated above, it is possible either to react the oximating agent, for example p-fluorobenzyloxyamine hydrochloride, with the compound (8) or with a corresponding compound in which the carboxy group is protected. Such a protected compound is conveniently obtained from the compound (7), for example by reaction with aqueous acid to give compound (8). Following reaction of the oximating agent with the -formyl group, the carboxy group is deprotected, for example by de-esterification using $KOH/CH_3OH/H_2O$. A similar choice with regard to the nature of the 5-substituent present in the reactant exists when the 6-substituent is a group -C(R)-O.

Modification of the 6-carboxyhex-2enyl group may be effected through the initial introduction of a modified group or by modification of this group during or at the end of the synthesis, ester formation conveniently being effected, for example, at the stage indicated hereinbefore and amides similarly being prepared by conventional procedures. Indeed, the procedures for effecting the various modifications indicated above will be apparent from the considerable literature existing on prostaglandin chemistry. Thus, for example one convenient route for the preparation of compounds containing a 6-carboxyhexyl group involves, in the case of the bicyclo [2,2,1] heptanes, the reduction of the compound (7) to saturate both double bonds. In the case of the bicyclo [2,2,1] hept -2Z- enes the corresponding 6-carboxyhexyl, 5-formyl compound may be obtained by the Diels Alder reaction of 8-carboxy-1-formyl-oct-1-ene and cyclopentadiene. (A separation of the two <u>trans</u> isomers obtained being required).

It will be appreciated that the methods described above are not the only ones which may be used for the preparation of compounds according to the present invention and that various alternative procedures may be used as will be apparent to those skilled in the art of prostaglandin chemistry.

It has been found that compounds according to the present invention inhibit the aggregatory activity of 15S-hydroxy-11α-9α-(epoxymethano)-prosta-5Z, 13E-dienoic acid [11, 9-(epoxymethano) PGH_2], which is a stable TXA_2 mimic, on human platelets in vitro. It is believed that such inhibition is the result of the compounds being thromboxane antagonists and the activity of the compounds is for convenience hereinafter discussed in these terms. Preferred compounds according to the present invention exhibit a pure antagonist activity. However antagonist and agonist activities have been found to be linked in some compounds and in consequence certain of the compounds have been found to show a partial agonist activity in certain tests, such as in the test based on the contractile activity of 11, 9-(epoxymethano) PGH_2 on the rabbit aorta strip, although they are antagonists in the platelet test. Structural features which tend to endow a compound with a more pure antagonist form of activity are (a) the absence of a halogen substituent, particularly at the para position, in the benzene ring of a phenoxyethyl O-substituted oxime; (b) the absence of a halogen substituent at the meta position of a benzyl O-substituted oxime; and (c) the presence of two benzene rings in the oxime substituent, these rings being located, for example, on a carbon atom joined directly to the oxygen atom of the oxime group. Some activity has also been alserved in compounds according to the present invention on guinea pig tracheal muscle.

Preferred compounds such as 5-endo-(6'-carboxyhex-2'Z-enyl)-6-exo-(O-p-fluorobenzyl-hydroxyiminomethyl)-bicyclo [2,2,1] hept-2Z-ene {5-endo-(6'-carboxyhex-2'Z-enyl)-6-exo(O-p-fluorobenzyl-carboxaldoxime)- bicyclo [2,2,1] hept-2Z-ene} are antagonists in the platelet test, block the aggregatory action of archidonic acid which is converted to TXA$_2$ by the platelet enzyme system and may or may not block the aggregatory action of ADP which acts via non-TXA$_2$- sensitive systems. Moreover, they are pure antagonists in the rabbit aorta strip test but do not block the contractile action of noradrenaline which acts on α-adrenoceptors.

Compositions according to the present invention are of interest for the treatment of thrombotic disorders and also for the treatment of anaphylactic disease states, for example as bronchodilators for the treatment of asthma, etc. They additionally have potential as anti-inflammatory agents. It will be appreciated that the spectrum of activity shown by any particular compound will vary and that certain compounds may be of particular interest in one of these applications whilst other compounds are of particular interest in another of them. Modifications of a compound can have other advantages. Thus, for example, it has been found that the ring unsaturated compounds described herein are usually less stable than the ring saturated compounds although the latter have similar activity in general. Furthermore the use of esters and others derivatives of the 6-carboxyhex-2-enyl group can have advantages in relation to slow release depot preparation through conversion in vivo to the active compound containing a free carboxy group, although the low water solubility of the esters must be taken account of.

It will be appreciated that compounds showing a partial enhancing action on thromboxane activity are also of some interest in respect of this activity although to a much lesser extent than with inhibitory activity. This, certain compounds according to the present invention may be of interest for laboratory or even for pharmaceutical purposes, for example in the control of bleeding by topical administration which avoids any systemic take-up, by virtue of the thromboxane enhancing facet of their activity which is shown under certain conditions.

The compounds may be formulated for use as pharmaceuticals for both animal and particularly human administration by a variety of methods, but usually together with a physiologically acceptable diluent or carrier. The compounds may, for instance, be applied as an aqueous or oily solutionor or as an emulsion for parenteral administration, the composition therefore preferably being sterile and pyrogen-free. The preparation of aqueous solutions of compounds in which the 5-substituent terminates in a free carboxy group may be aided by salt formation. The compounds may also be compounded for oral administration in the presence of conventional solid carrier materials such as starch, lactose, dextrin and magnesium stearate. Alternative formulations are as aerosols, suppositories, cachets, and, for localised treatment, as suitable creams or drops. Without commitment to a rigid definition of dosage, which is difficult in view of the different levels of activity, methods of formulation, and methods of administration, some general guidance may be given. In the case of systemic administration to produce a thromboxane antagonism the normal daily dosage which is proposed lies in the range from about 0.1 mg to about 10 mg per kilogram (the average weight of a human being about 70 kg) and particularly from about 1 mg to about 5 mg per kilogram. It will be appreciated, however that dosages outside this range may be considered, for example in the case of topical application to produce a localised thromboxane agonism, and that the daily dosage may be divided into two or more portions.

The inventions illustrated by the following Examples.

EXAMPLES

Although the various compounds have predominantly the isomeric form indicated, some minor contamination by other isomers, particularly by the 5-endo, 6-endo isomer, may be present. The numbering used for the sub-sections of Example 1 is in accordance with that used in the reaction schene on page 38 of the specification. In Example 2 sub-sections relating to the analogues ring saturated compounds have been similarly numbered.

Example 1: 5-endo-(6'-Carboxyhex-2'Z-enyl) 6-exo-(O-p-fluorobenzylhydroxyiminomethyl)-bicyclo [2,2,1] hept-2Z-ene

(1) Maleinaldehydic acid pseudo-ethyl ester

30 g of redistilled furan-2-aldehyde is mixed with 600 ml dry ethanol and 300 mg of methylene blue is added. Dry air is blown gently through the solution and the material is irradiated with a 300 W tungsten lamp for about two days until t.l.c. in a silica gel/ether system shows essentially no remaining starting material. The solution is then stirred with vanadium pentoxide for four hours, filtered, and the solvent removed under reduced pressure. The residual oil is distilled under high vacuum to give the title coopound as an oil (23.6g, 76%), b.p. 90-92°C/0. 2mm.

(2) Diels Alder reaction between maleinaldehydic acid pseudo-ethyl ester and cyclopentadiene

Freshly cracked cyclopentadiene (9.0g) is mixed with 11.0g of the pseudo ester (1). A gentle warming is observed and the mixture is allowed to stand overnight. The N.M.R. spectrum typically shows the formation of the adduct (2) to be complete and the material is taken to the next step without purification.

(3) 5-endo-Carboxyethyl-6-exo-diethoxymethyl-bicyclo [2,2,1] hept-2Z-ene

The Diels-Alder adduct (2) (10g) is heated in a mixture of triethyl orthoformate (10 ml), dry ethanol (100 ml) , and concentrated sulphuric acid (1 ml). The mixture darkens and after 12 hours is cooled and treated with anhydrous potassium carbonate (5g) and ether (150 ml). Water is then slowly added with efficient mixing to neutralise the acid. The product is extracted with ether, washed with water and distilled to give the title compound as an oil (7.3g, 63%) b.p. $115-120^{\circ}C/0.3$mm.

(4) 5-endo-Hydroxymethyl-6-exo-diethoxymethyl-bicyclo [2,2,1] hept-2Z-ene

The ester (3) is added in ether to lithium aluminium hydride (10% excess))in ether with stirring at reflux temperature. After the addition, the mixture is boiled for a further 1 hour. The reaction is quenched with wet ether and then 5% aqueous sodium hydroxide to precipitate aluminium. The colourless organic phase is filtered, dried over anhydrous potassium carbonate, and the resulting alcohol (85 - 90% yield) used directly in the next stage.

(5) 5-endo-Cyanomethyl-6-exo-diethoxymethyl-bicyclo [2,2,1] hept-2Z-ene

The alcohol (4) (7g) in 15 ml dry pyridine is added slowly at 0°C to p-toluenesulphonyl chloride (7.5 g) in pyridine (45 ml). The mixture is kept overnight at 10°C and then quenched by pouring over ice with vigorous shaking. The product is extracted with ether, washed consecutively with water, 0.1 M sodium carbonate and brine, and then dried (K_2CO_3) and the solvent removed to give the tosylate ester of the alcohol as a colourless oil in high yield.

The tosylate ester (12 g) in dimethyl sulphoxide (15 ml) is added with stirring to potassium cyanide (3 g) in dimethyl sulphoxide (20 ml). The mixture is heated to 100°C under nitrogen for 6 hours and is then cooled, poured into water and the product taken into ether. The solvent is removed and the residue distilled to give title compound as an oil (6.6 g, 88%), b.p. 112-124°C/1.8mm.

(6) 6-exo-Diethoxymethyl-bicyclo [2,2,1] hept-2Z-en-5-endo-methylcarboxyaldehyde

Di-isobutylaluminium hydride (25 ml of 1M solution in hexane) is added with strirring over a 10 minute period to the cyano compound (5) (5.0 g) in dry toluene (70 ml) at -15°C under nitrogen. After a further 1 hour at room temperature the reaction is terminated by the additon with caution of methanol (6 ml), followed by saturated aqueous sodium hydrogen tartrate (95 ml). The mixture is then stirred and heated at 40°C for two hours. The organic phase is separated and the aqueous layer is further extracted with ethyl acetate, the combined organic solutions being dried and stripped of solvent to give the product as a yellow oil. Chromatography on Florisil in benzene gives the pure title compound as a colourless oil (3.2 g, 63%), ν (film): 1725 cm^{-1}.

(7) 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-diethoxymethyl-bicyclo [2,2,1] hept-2Z-ene

(4-Carboxy-n-butyl)-triphenylphosphonium bromide (7.0 g) is dried at 75°C under vacuum for 90 minutes. The white solid is cooled, the vacuum is released to dry nitrogen and 10 ml of dimethyl sulphoxide (10 ml) is added followed by 15 ml of a 2M solution of dimesyl sodium in dimethyl sulphoxide. The temperatue is maintained at 25°C and the aldehyde (6) (1.5 g) is added to to the deep red yield solution. After stirring overnight the solvent is removed at 55-60°C under vacuum. The residue is dissolved in water, extracted with ether, and the aqueous phase carefully acidified to pH 4 with 2N HCl. The mixture is extracted with ether and the ethereal solution dried and concentrated to give the title compound as an oil (1.34 g, 66%).

(8) 5-endo-(6'-Carboxymethylhex-2'Z-enyl)-6-exo-formyl-bicyclo [2,2,1] hept-2Z-ene

The acid acetal (7) (5g) in ether is treated with excess ethereal diazomethane to form the methyl ester and then the ketal protecting group is removed by dissolving the compound in 215 ml chloroform and adding concentrated hydrochloric acid

(55 ml) to form a two-phase system. The mixture is extracted with ether and the ethereal solution dried and concentrated to give the title compound as an oil (3.38g, 90%).

<u>Note</u>: care should be taken to avoid contact of this compound with methanae since it very readily forms the dimethyl acetal.

(9) <u>5-endo-(6'-Methoxycarbonyl-hex-2'Z-enyl)-6-exo-(O-p-fluorobenzyl-hydroxyiminomethyl)-bicyclo [2,2,1] hept-2Z-ene</u>

The aldehyde/ester (8) (100 mg) is heated with p-fluorobenzyloxyamine hydrochloride (100 mg) in dry pyridine (5 ml) for 3 hours at 60°C. The pyridine is removed in vacuo, the residue is partitioned between water and diethyl ether and the ether phase is evaporated to dryness. The product is purified by liquid-gel partition chromatography using a 400 x 15 mm column of Sephadex LH20 (Pharmacia) substituted with Nedox 1114 olefin oxide (Ashland Chemical Co. USA) to 50% w/w and eluting with hexane/dichlorethane (90:10v/v) at a flow rate of 12 ml/hour. The chromatography gives the title compound as an oil:

The p-fluorobenzyloxamine hydrochloride is prepared as follows.

N-Hydroxyphthalimide (12.0 g) in 130 ml dimethyl sulphoxide is treated with anhydrous finely divided potassium carbonate (6.6 g), when the dark red colour of the anion develops. The mixture is then treated dropwise at room temperature with p-fluorobenzyl chloride (20 g) and the mixture is stirred overnight or until the red colour is discharged. The reaction mixture is poured into water, and the resultant crystalline product is filtered off. Recrystallisation from ethanol gives N'-p-fluorobenzyloxyphthalimide in pure form as white needles. (16.4 g, 82%), m.p. 156-157°C.

The imide (13.5g) is boiled in 400 ml ethanol with 99% hydrazine hydrate (2.5 g) for 2 hours. The mixture is cooled, 7 ml of conc. hydrochloric acid is added and the precipitate of phthalhydrazide is removed by filtration. The solutuion is concentrated to dryness and the salt taken up in water, washed with ether and then basified. The free base is taken into ether to give an ethereal solution which is washed with brine and then dried ($MgSO_4$). Dry hydrogen chloride gas is passed into the ethereal solution to deposit pure p-fluorobenzyloxyamine hydrochloride which is recrystallised from ethanol as white plates (7.9g, 90%), m.p. 298-300°C.

(9') 5-endo-(6'- Carboxyhex-2'Z-enyl)-6-exo-(O-p-fluorobenzylhydroxyiminomethyl)-bicyclo [2,2,1] hept-2Z-ene

Ester cleavage in compound (9) is effected by heating in aqueous methanol with potassium hydroxide (0.1N) for 3 hours at 40°C. The product is again purified by liquid-gel chromatography but using a 400 x 15 mm column of Sephadex LH20 substituted with Nedox 1114 olefin oxide to 20% w/w and eluting with dichloroethane/hexane/ethanol (100:100:5 v/v/v) containing 0.1% v/v of acetic acid at a flow rate of 12 ml/hour. The chromatography gives the title compound as an oil in 50-60% overall yield from compound (8); λ_{max} (CH_3OH) 263 nm, ε_{max} 625 ; M.S. (methyl ester): M^+ 371.

Example 2: 5-endo(6'-Carboxyhex-2'Z-enyl)-6-exo-(O-p-fluorobenzyl-hydroxyiminomethyl)-bicyclo [2,2,1] heptane

(1), (2), (3) 5-endo-Carboxyethyl-6-exo-diethoxymethyl-bicyclo [2,2,1] - hept-2-ene

Maleinaldehydic acid pseudo-ethyl ester is prepared as described in Example 1 (1) and reacted with cyclopentadiene in a Diels Alder reaction as described in Example 1 (2). The Diels Alder adduct is treated with ethanol under acidic conditions as described in Example 1 (3) to give 5-endo-carboxyethyl-6-exo-diethoxymethyl-bicyclo [2,2,1] -hept-2Z-ene.

(3A) 5-endo-Carboxyethyl-6-exo-diethoxymethyl-bicyclo [2,2,1] - heptane

5-endo-Carboxyethyl-6-exo-diethoxymethyl-bicyclo [2,2,1] -hept-2Z-ene (30 g) is dissolved in 200 ml of ethanol and 0.3 g of 10% palladium on charcoal is added. The mixture is vigorously stirred in 1 atmosphere of hydrogen gas at room temperature. 1 molar equivalent of hydrogen gas is absorbed and the product is then isolated by removal of the catalyst by filtration through a Celite pad, followed by evaporation of the filtrate to give a quantitive yield of the title compound as an oil, b.p. 105-110°C/1.5 mm.

(4) 5-endo-Hydroxymethyl-6-exo-diethoxymethyl-bicyclo [2,2,1]-heptane

The ester (3A) (27 g) is added in ether to a 10% excess of lithium aluminium hydride (2.1 g) in ether with stirring at reflux temperature. The mixture is boiled for 1 hour after the addition and is then quenched by the addition of wet ether followed by 5% aqueous sodium hydroxide to precipitate aluminium salts. The colourless organic phase is dried over magnesium sulphate, filtered and evaporated to give the title compound as an oil (20 g, 91%).

(5) 5-endo-Cyanomethyl-6-exo-diethoxymethyl-bicyclo [2,2,1]-heptane

The alcohol (4) (20 g) in a minimum volume of dry pyridine is added slowly to 20 g of p-toluenesulphonyl choride in 130 ml dry pyridine with stirring at 0°C. The mixture is kept at 5°C overnight and then poured into a water/ice mixture. The resulting precipitate is filtered off and dried to give the tosylate ester of the alcohol in 85% yield as an off-white solid, m.p. 84-86°C (dec).

The tosylate (14 g) in 15 ml dimethyl sulphoxide is added to 5 g of dry potassium cyanide in 20 ml dimethyl sulphoxide. The mixture is stirred under nitrogen and the temperature slowly raised over 1 hour to 110°C. After 5 hours the reaction mixture is cooled and poured into water. The product is isolated by ether extraction, and purified by distillation to give the title compound (7.8 g, 90%), b.p. 115- 126°C/1.5 mm.

(6) 6-exo-Diethoxymethyl-bicyclo [2,2,1] heptane-5-endo methylcarboxaldehyde

The cyano compound (5) (20 g) is stirred at -15°C in 200 ml dry toluene under nitrogen. Di-isobutylaluminium hydride (113 ml of a 1M solution in hexane) is added to the substrate over 25 minutes and the mixture allowed to reach room temperature. After 1 hour, methanol (30 ml) is cautiously added, followed by 400 ml of saturated aqueous sodium hydrogen tartrate. The mixture is stirred and heated at 40°C for 2 hours. The upper organic layer is separated and the aqueous phase further extracted with ethyl acetate. The combined organic solutions are dried ($Mg\ SO_4$) and the solvent removed to give a yellow oil. This is chromatographed on Florisil in benzene to give the pure title compound as a colourllss oil (17.2 g, 85%), (film): 1725 cm^{-1}.

(7) 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-diethoxymethyl-bicyclo [2,2,1] heptane

(4-Carboxy-n-butyl)-triphenylphosphonium bromide (23.3 g) is dried at 75°C under vacuum for 2.5 hours. The resulting white solid is then cooled, the vacuum released to dry nitrogen, and 30 ml of dimethyl sulphoxide is added. A 2M solution of dimesyl sodium in dimethyl sulphoxide (50 ml) is added slowly while the mixture is maintained at 25°C with a water bath. After 15 minutes the aldehyde (6) (5.0 g) is added to the deep red ylide thus produced. The mixture is stirred overnight and then the solvent is removed at 55-60°C under vacuum. The residue is dissolved in water, and the aqueous phase is extracted with ether and is then carefully acidified to pH4 with 2N HCl. The precipitate is extracted into ether and the ethereal solution is dried and concentrated to give the title compound as an oil 3.7 g, 55%).

(8') 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-formyl-bicyclo [2,2,1] heptane

The acid acetal (7) (1.8 g) is dissolved in 200 ml chloroform and 50 ml of concentrated hydrochloric acid is added to form a two phase system. The mixture is vigorously stirred for 90 minutes and then extracted with ether and the ethereal solution dried and concentrated. The residual oil is purified by silicic acid chromatography, the oil being applied to the column (prepared by slurrying 10 g of Unisil silicic acid - Clarkson Chemical Co. USA - in hexane and pouring into a glass chromatography column) in hexane and elution being carried out with increasing proportions of diethyl ether in hexane up to pure diethyl ether. The chromatography gives the title compound as a colourless oil (1.4 g, 83%), ν (film): 795, 1715 (broad), 2700cm^{-1}; δ (90mHz, $CDCl_3$) 1.2 to 2.6 (18H,m), 5.4 (2H,m), 9.6 (1H,d).

Note: Care should be taken to avoid contact of this compound with methanol since it very readily forms the dimethyl acetal.

(9') 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-(O-p-fluorobenzyl-hydroxyimonomethyl)-bicyclo [2,2,1] heptane

The aldehyde/acid (75 mg) is heated with 100 mg of p-fluorobenzyloxyamine hydrochloride [prepared as described in Example 1 (9)] in dry pyridine (5 ml) for 1 hr. The pyridine is removed in vacuo, and the residue partitioned between water and diethyl ether. The ether phase is evaporated to dryness and the resulting product is purified by liquid-gel partition chromatography using a 400 x 15 mm column of Sephadex LH 20 substituted with Nedox 1114 olefin oxide to 20% w/w and eluting with dichloroethane/hexane/ethanol (100:100:5 v/v/v) containing o.1% v/v of acetic acid at a flow rate of 12 ml/hour. The chromatography gives the title compound as a colourless oil (50 mg), λ_{max} (CH_3OH) 263 nm, ε_{max} 650; M.S: M^+ (methyl ester) 373.

Example 3: 5-endo (6'-Carboxyhex-2'Z-enyl)-6-exo-(O-p-fluorobenzyl-1'-hydroxy-iminoethyl)-bicyclo [2,2,1] heptane

(1) 5-endo(6'-Carboxyhex-2'Z-enyl)-6-exo-(1'-hydroxyethyl) bicyclo [2,2,1] heptane

5-endo-(6'-carboxyhex-2'Z-enyl)-6-exo-formyl bicyclo[2,2,1] heptane is prepared as described in Example 1(8). This aldehyde (250 mg, 1mmole) is dissolved in dry tetrahydrofuran (10 ml) at 0°C and treated under nitrogen un with stirring over 30 minutes with a 1M solution of methyl magnesium iodide in ether (2 ml). The mixture is stirred under nitrogen overnight whilst is is allowed to come to room temperature. The reaction is then quenched by the addition of dilute aqueous hydrochloric acid and the product is extracted with ether (3x), the ether solution is dried and evaporated to give the title compound as an oil (200 mg).

A small sample is treated to form the Me ester trimethylsilyl ether and on gas chromatography mass spectroscopy on a 3% OVI column this shows a carbon value of 18.2, a M^+ value of 352 and a base peak at 117. Chromatography on a substituted Sephadex LH20 column as used in Example 2 (9') of the bulk of the oily product using a mixture of (all preparations by value) 100 parts of hexane, 100 parts of 1,2-dichloroethane, 5 parts of ethanol and 0.1% of the total of glacial acetic acid, as eluant yields the isomeric secondary alcohols differing in the configuration at the newly introduced asymmetric carbon atom $(-\overset{*}{C}HOH.CH_3)$. Nmr spectroscopy on these isomeric products in $CDCl_3$ gives the following δ values:

First isomer eluted: 7.3 (s. broad, 1H, OH); 5.45(m., 2H, olefinic H)· 3.6 (m-qxd; 1H, -CHOH), 2.5-1.0; (m, 21H, olefinic H); 1.2 (d, CH_3 discernible).

Second isomer eluted; 7.8(s. broad, 1H, OH); 5.4(m., 2H, olefinic H); 3.55(m-qxd, 1H-CHOH); 2.5-1.0(m, 18H, aliphatic H); 1.2(d, CH_3 discernible).

(2) 5-endo(6'-Carboxyhex-2'Z-enyl)-6-exo-acetyl-bicyclo [2,2,1] heptane

The procedure described under (1) is repeated with 600 mg of the aldehyde to give a mixture of the two isomeric alcohols (500 mg). This mixture is dissolved in pure acetone (15 ml) and the solution is cooled to 0°C. Jones reagent (600 μl of a solution prepared by dissolving 26.7 g of chromic anlydride in 23 ml of concentrated sulphuric acid and diluting to 100 ml with water, followed by filtration) is added slowly to the cooled solution with vigorous stirring over 15 minutes. After a further 10 minutes stirring at 0°C. the mixture is poured into water and the product extracted with ether. The ether solution is dried and evaporated to give the title compound as an oil (~75% overall yield from the formyl compound) The methyl ester derivative on gas chromatography mass spectroscopy on a 3% OVI column i.e. exhibits a carbon value of 17.15, a M+ value of 278 and a base peak of 43/137 NMR spectroscopy in $CDCL_3$ gives the following δ values. 10.0(s-broad, 1H,CooH); 5.4(m,2H,olefinic H); 2.8-1.1(m,21H,aliphatic H); 2.2(s,CH_3-CO,discernible).

(3) 5-endo(6'-Carboxyhex-2'Z-enyl)-6-exo-(O-p-fluorobenzyl-1'-hydroxyiminoethyl)-bicyclo[2,2,1] heptane

The ketone (100 mg) prepared as described in (2) is heated with p-fluorobenzyloxyamine hydrochloride (100 mg) in dry pyridine (5 ml) at 60°C for 2 hours. The pyridine is removed in vacuo and the residue is partitioned between water (pH 4) and diethyl ether. The ether is removed in vacuo to give an oil which is purified by liquid-gel partition chromatography on a column of Sephadex LH 20 substituted with Nedox 1114 olefin oxide to 20% w/w, eluting with dichloroethane/hexane/ethanol (100:100:5 v/v/v) containing 0.1% v/v of acetic acid. The chromatography gives the title compound as an almost colourless oil (90 mg),$\lambda_{max}(CH_3OH)$263 nm,ε_{max} 620; M.S. (methyl ester) ester):M+ 401; $\delta(CDCl_3)$ 1.85 (s, about 3H, methyl H), 5.00 (s, 2H, benzyl H), 5.30 (m, 2H, olefinic H), 6.9-7.5 (m, 4H, aromatic H).

Example 4: 5-endo (6'-Carboxyhex-2'Z-enyl)-6-exo-(O-p-fluorobenzyl-α-hydroxyiminobenzyl)-bicyclo [2,2,1] heptane

(1) 5-endo(6'-Carboxyhex-2'Z-enyl)-6-exo-(α-hydroxybenzyl)-bicyclo [2,2,1] heptane

5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-formyl-bicyclo [2,2,1] heptane is prepared as described in Example 1(8). This aldehyde (800 mg) is reacted with 2 equivalents of phenyl magnesium bromide in a similar manner to that described for the reaction with methyl magnesium bromide in Example 3. The title compound is obtained as a mixture (900 mg) of the two isomeric secondary alcohols differing in the configuration at the newly introduced carbon atom ($-\overset{*}{C}HOH.C_6H_5$). Gas chromatography mass spectroscopy on the methyl ester trimethylsilyl ether derivative of a small sample of the mixture of alcohols on a 3% OVI phase at 230°C gives a carbon value (equivalent carbon value relative to retention time of methyl esters of straight chain fatty acids) of about 22, the peak being broad due to a partial separation of the isomers, a M^+ value of 414 with a major ion (M-90) at 324 and a base peak of 179 (C_6H_5CH-OTMS). A n.m.r. spectrum of the mixture of alcohols in $CDCl_3$ gives the following δ values: 7.3 (m, 5H, aromatic H), 5,4-5.0 (m, 4H, olefinic H), 4.4-4.2 (d, 1H, CHOH), 2.6-1.0 (m, 18H, aliphatic H).

(2) 5-endo (6'-Carboxyhex-2'Z-enyl)-6-exo-benzoyl-bicyclo [2,2,1] heptane

The mixture of the two isomeric alcohols (1) (900 mg) is dissolved in pure acetone (15 ml) and the solution is cooled to 0°C.

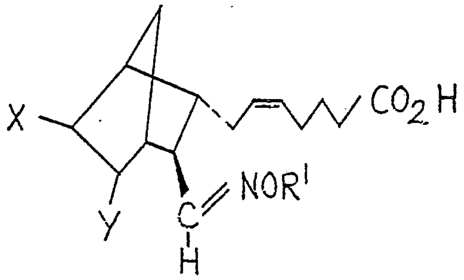
The solution is then treated with Jones reagent (1 ml, prepared as described in Example 3) and oxidation of the alcohol effected according to the procedure described in Example 3 to give the title compound as an oil. Gas chromatography mass spectroscopy on the methyl ester derivative of a small sample of the ketone on a 3% OVI phase at 240°C gives a carbon value of 23.65, a M^+ value of 340 with a major ion at 105 ($C_6H_5CO^+$) and a base peak (M-141) at 199. A n.m.r. spectrum of the ketone in $CDCl_3$ gives the following δ values: 8.1-7.9 (m, 2H, ortho aromatic H), 7.6-7.1 (m, 4H, meta and para aromatic H), 5.3 (m, 2H, olefinic H), 2.8-1.1 (m, 18H, aliphatic H) and an i.r. spectrum (film) gives ν values as follows: 1730 (sh), 1705, 1675, 1595 and 1575 cm-1.

(3) 5-endo(6'-Carboxyhex-2'Z-enyl)-6-exo-(O-p-fluorobenzyl-α-hydroxyiminobenzyl)-bicyclo [2,2,1] heptane

The ketone (2) is reacted with p-fluorobenzyloxyamine hydrochloride in dry pyridine according to the procedure described in Example 3 and the reaction mixture worked up as described therein to give the title compound.

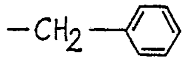
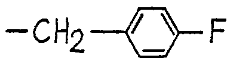
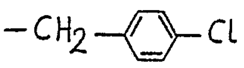
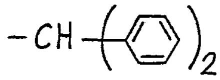
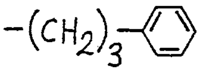
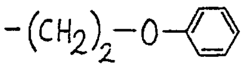
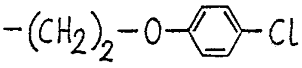
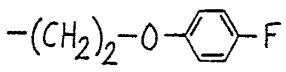
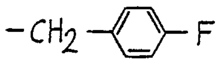
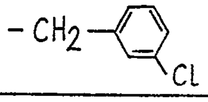
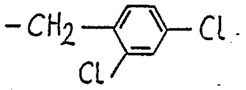
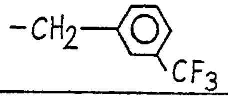
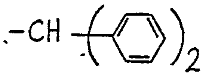
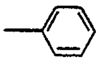
Example 5: 5-endo-(6'-Carboxyhex-2'Z-enyl) bicyclo [2,2,1] hept-2Z-enes and heptanes containing other 6-exo substituents

The compounds of formula



listed in Table 1 below are prepared as described in Example 1 (for ring unsaturated compounds) or as described in Example 2 (for ring saturated compounds) using the appropriate oximating agent. This agent may however either be reacted with a precursor in which the carboxy group is protected as in Example 1 or it is in the free state as in Example 2. For the purposes of comparison, data on the compounds of Examples 1 and 2 has also been included in this table. The UV data relates to the main peak or peaks of the spectrum of the free acid in methanolic and the MS data, unless otherwise indicated, relates to the value obtained for the methyl ester by gas chromatography mass spectroscopy. (The methyl esters are prepared by dissolving the free acid in methanol, using warming and the additon of an excess of ethereal diazomethane to the metholie solution, standing, and the removal of the solvent).

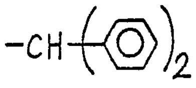
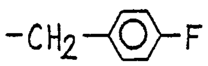
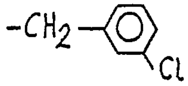
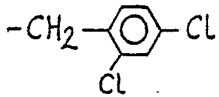
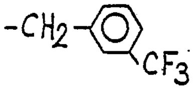
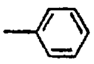
The compounds of the present application are related to those of the copending application of even date herewith in our names in which the group $= NOR'$ is replaced by a group $= N.NHCO(NH)_aR'$, in which _a_ may be 0 or 1. Further exemplification of groups R' is to be found in that application.

COMPOUND		U.V. DATA		M.S. DATA
XY	R'	λ_{max} nm	ε_{max}	(Methyl ester) M^+
=		257	370	367
=		263	625	385
=		267	270	401/3
=		258	450	(1)
=		261	270	295
=		271	1450	397
=		281	1550	431/433
=		279	1320	415
H,H		263	650	387
H,H		267	350	403/405
H,H		272	380	437/439/441
H,H		263	605	437
H,H		258	405	(1)
H,H	$(CH_2)_4CH_3$	No U.V.	Chromophore	349
H,H		234 272	10400 1790	341 (2)

(1) M^+ not apparent: ion at 167 $(C_6H_5)_2CH+$

(2) Free acid by direct inlet.

N.m.r. data on the bicyclo [2,2,1]heptane compounds (XY is H,H) of Table 1 is presented in Table 2 below: All of the δ values relate to $CDCl_3$ solution and are referred to $(CH_3)_4Si$.

COMPOUND R'	Ethylenic protons of substituent at 5-position of ring	Proton of aldoxime group (1)	R' Protons	
			aliphatic (2)	aromatic
	5.30 (m) 2H	6.6 (d)	6.20 (s) 1H	7.35 (m) 10H
$-(CH_2)_4CH_3$	5.35 (m) 2H	6.5 (d)	4.00/4.05 (t) 2H	–
	5.35 (m) 2H	6.5 (d)	5.00/5.05 (s) 2H	6.9 - 7.4 (m) 4H
	5.30 (m) 2H	6.55 (d)	5.00/5.05 (s) 2H	7.1 - 7.4 (m) 4H
	5.30 (m) 2H	6.55 (d)	5.10/5.15 (s) 2H	7.1 - 7.5 (m) 3H
	5.35 (m) 2H	6.80 (d)	5.10/5.15 (s) 2H	7.4 - 7.7 (m) 3H
	5.40 (m) 2H	7.65 (d)	–	6.9 - 7.5 (m) 5H

(1) Only the signal corresponding to the proton of one of the isomers (syn and anti) is observed as the signal corresponding to the proton of the other isomer is obscured by the signal corresponding to the aromatic R' protons, the strenth of the signal is therefore less than 1H.

(2) The signals corresponding to these protons in the two isomers overlap and cannot be separately recorded.

Example 6: 5-endo-(6'-Carboxyhexyl)-6-exo-(O-p-fluorobenzyl-hydroxyiminomethyl)-bicyclo [2,2,1] heptane

(1) 5-endo(6'-Carboxyhexyl)-6-exo-formyl-bicyclo [2,2,1] heptane

5-endo-(6'-Carboxyhexyl)-2'Z-enyl)-6-exo-diethoxymethyl-bicyclo [2,2,1] heptane is prepared as described in Example 2 (7). This acid/acetal (300 mg) is stirred with 10% palladium charcoal (50 mg) in absolute ethanol (10 ml) for 30 minutes whilst continuously passing hydrogen gas through the suspension. The catalyst is removed by filtration through a Whatman No.550 filter disc and the ethanol is then removed in vacuo. The oily residue of 5-endo(6'-carboxyhex-2'Z-enyl)-6-exo-diethoxymethyl-bicyclo [2,2,1] heptane is dissolved in $CHCl_3$ (50 ml), 2N aqueous hydrochloric acid (50 ml) is added, and the two phase system is stirred for 6 hours at room temperature. Water (100 ml) is then added, followed by diethyl ether (150 ml) and after vigorous shaking the organic phase is separated. The aqueous phase is extracted with a further 150 ml of diethyl ether and the two ether extracts are combined. Evaporation of the diethyl ether from the dried solution gives 5-endo(6'-carboxyhexyl)-6-exo-formyl-bicyclo [2,2,1] heptane as an oil (152 mg), ν (film 1715 cm^{-1} (broad); M.S. (methyl ester): $M^+/M^+{+}1$ 266/267 - single peak;

δ ($CDCl_3$) 1.1-2.6 (22H, aliphatic H), 9.6 (d, 1H, $C\underline{H}O$), 10.0 (broad, $COO\underline{H}$).

(2) 5-endo(6'-Ccarboxyhexyl)-6-exo-(O-p-fluorobenzyl-hydroxyiminomethyl)-bicyclo [2,2,1] heptane

The aldehyde/acid (1) (50 mg) is reacted in dry pyridine with p-fluorobenzyloxyamine hydrochloride according to the procedure described in Example 2 (9') and the reaction mixture is worked up according to the procedure described therein to give the title compound as an oil (49 mg, 66%, after chromatography), λ_{max} (CH_3OH) 263 nm, ε_{max} 720; M.S.(methyl ester): M^+389.

Example 7: 5-endo(6'-Carboxyhexyl)-6-exo-(O-diphenylmethyl-hydroxyiminomethyl)-bicyclo [2,2,1] heptane

5-endo(6'-Carboxyhexyl)-6-exo-formyl-bicyclo [2,2,1] heptane (50 mg), prepared as described in Example 6 (1), is reacted in dry pyridine with diphenylmethyloxyamine hydrochloride according to the procedure described in Example 2 (9') and the reaction mixture is worked up according to the procedure described therein to give the title compound as an oil (50 mg, 58% after chromatography), λ_{max} (CH_3OH) 248 nm, ε_{max} 415, M.S. (methyl ester):M^+ not apparent, the spectrum being dominated by the m/e 167 ion; δ ($CDCl_3$) 6.15 (s, 1H, $\underline{CH}$ $(C_6H_5)_2$), 6.55 (d, about 0.5H, $>\underset{H}{C}=N$, other isomer not detectable), 7.30 (m, 10H, aromatic H).

Example 8: Tests of Biological Activity

Various of the compounds described in Examples 1 to 7 are tested for biological activity in the human platelet and rabbit aorta systems.

Human Platelet System

Platelet-rich plasma obtained from fresh, citrated human blood. Addition of the 11,9-epoxymethano analogue of PGH_2 ($1 \times 10^{-7}M$) causes immediate aggregation recorded as an increase in light transmission (600 nm). In a second experiment the individual compounds are added 5 minutes previously to addition of the PGH_2 analogue. The dose of the PGH_2 analogue added is then increased to a level which gives a similar response to that obtained in the absence of antagonist. The affinity constant, K_B, for the compound is calculated according to the Gaddum-Schild Equation (based on Law of Mass Action).

$$DR-1 = [B] \times K_B$$

DR = dose ratio

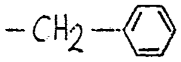
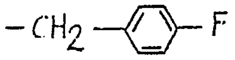
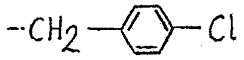
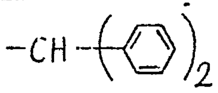
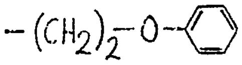
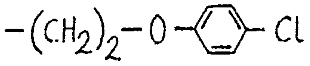
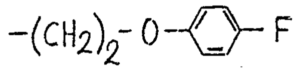
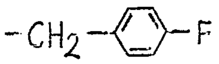
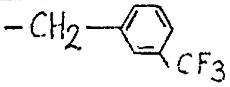
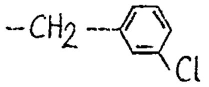
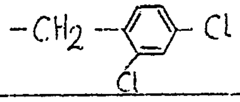
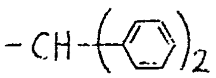
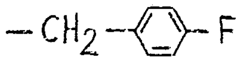
$[B]$ = molar concentration of compound

Rabbit Aorta System

Spiral strips of thoracic aorta are suspended in Kreb's-Henseleit solution and aerated with 95% O_2/5% CO_2 at 37°C. Tension changes are recorded with a Grass FT03 force transducer.. Initially, cumulative dose response curves to 11,9-(epoxymethano) PGH_2 (2×10^{-9}, 1×10^{-8}, 5×10^{-8} and $2.5 \times 10^{-7}M$) are obtained. In a second experiment the individual compounds are added 30 minutes previously to the addition of the series of agonist doses. Affinity constants are calculated as above.

Results typical of those obtained for the various compounds (all of which are of the formula shown at the beginning of Example 5 except where otherwise indicated) are shown in Table 3. As a standard of comparison, the affinity constant of the potent muscarinic receptor antagonist atrophine is 1 x 10^9 litres/mole.

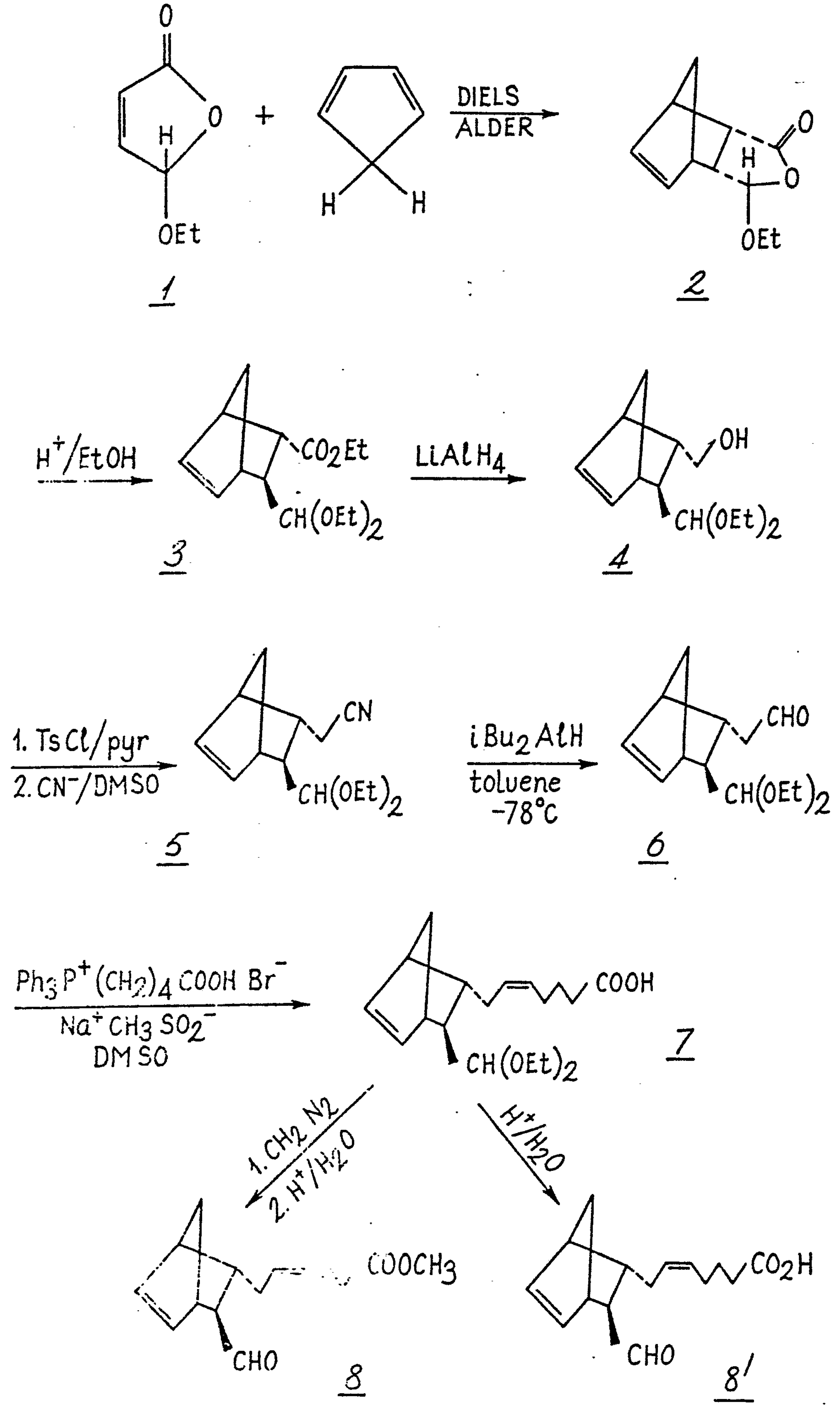
Table 3

	COMPOUND	AFFINITY CONSTANTS x 10^{-5} litres/mole	
X, Y	R'	Human Platelets	Rabbit Aorta
=		1.9	15
=		4.0	36
=		2.1	67
=		510 (1)	5.9
=		0.50	25
=		1.0	(2)
=		0.4	(2)
H,H		5.8	23
H,H		-	(2)
H,H		5.9	(2)
H,H		2.8	42
H,H		480 (1)	1.9
H,H	$-(CH_2)_4CH_3$	1.7	1.5
H,H (3)		0.83	-

(1) significant antagonism of ADP and thrombin is shown by these two substances; $K_B(ADP) = 190 \times 10^5$. The other compounds do not block ADP, having $K_B(ADP)$ of $< 0.25 \times 10^5$.

(2) Partial agonist.

(3) Double bond in substituent at 5-postion of ring is also reduced in this compound.


O
O
H
OEt
+
H
H
DIELS
ALDER
O
H
O
OEt
1
2
H+/EtOH
CO2Et
CH(OEt)2
LiAlH4
OH
CH(OEt)2
3
4
1. TsCl/pyr
2. CN-/DMSO
CN
CH(OEt)2
iBu2AlH
toluene
-78°C
CHO
CH(OEt)2
5
6
Ph3P+(CH2)4COOH Br-
Na+CH3SO2-
DMSO
COOH
CH(OEt)2
7
1. CH2N2
2. H+/H2O
H+/H2O
COOCH3
CHO
8
CO2H
CHO
8′

CLAIMS

1. A compound being a bicyclo [2,2,1] heptane or hept-2Z-ene which is substituted at the 5-position by a 6-carboxyhex-2-enyl group or a modification thereof as defined herein, and at the 6-position by an aldoxime or ketoxime group which is O-substituted by an aliphatic hydrocarbon residue, an aromatic residue, or an aliphatic hydrocarbon residue substituted directly or through an oxygen or sulphur atom by an aromatic residue.

2. A compound according to Claim 1 in which the substituent at the 5-position is a 6-carboxyhex-2-enyl group or a derivative thereof formed at the carboxy group.

3. A compound according to Claim 1, in which the substituent at the 5-position is a 6-carboxyhexyl group or a derivative thereof formed at the carboxy group.

4. A compound according to Claim 2 or 3, in which the derivative is an amide, an ester or a salt of the carboxy group.

5. A compound according to Claim 1, in which the substituent at the 6-position is an O-substituted aldoxime group.

6. A compound according to Claim 1 in which the substituent at the 6-position is an O-substituted ketoxime group which has an aliphatic hydrocarbon residue, an aromatic residue, or an aliphatic hydrocarbon residue substituted directly or through an oxygen or sulphur atom by an aromatic residue linked to the carbon atom thereof.

7. A compound according to Claim 6, in which the O-substituted ketoxime group has an aliphatic hydrocarbon residue, an aromatic residue or an aliphatic hydrocarbon residue substituted directly by an aromatic residue linked to the carbon atom thereof.

8. A compound according to Claim 7, in which the aldoxime or ketoxime group is O-substituted by an aliphatic hydrocarbon or an aromatic residue.

9. A compound according to Claim 7, in which the aldoxime and ketoxime group is O-substituted by an aliphatic hydrocarbon residue substituted directly or through an oxygen or sulphur atom by a phenyl group or a substituted phenyl group.

10. A compound according to Claim 9, in which the aliphatic hydrocarbon residue is of 1 to 3 carbon atoms when substituted directly and of 2 or 3 carbon atoms when substituted through an oxygen or sulphur atom.

11. A compound according to Claim 9 or 10, in which the aliphatic hydrocarbon residue is substituted directly or through an oxygen or sulphur atom by a phenyl group or by a phenyl group having one or more substituents selected from alkoxy and amino groups and halogen substituents.

12. A compound according to Claim 11, in which said substituent(s) are chloro, fluoro or trifluoromethyl.

13. A compound according to Claim 7 in which the aldoxime or ketoxime group is O-substituted by an aliphatic hydrocarbon residue substituted by at least two aromatic residues.

14. A compound according to Claim 13 wherein the aliphatic hydrocarbon residue is substituted directly by two phenyl or substituted phenyl groups.

15. A compound according to Claim 9 or 10, in which substitution of the phenyl group is limited to the ortho and para positions when the hydrocarbon residue is directly substituted and to the ortho and meta positions when it is substituted through an oxygen or sulphur atom.

16. A compound according to Claim 1, in which the configuration about any double bond in the 5-substituent is <u>cis</u>.

17. A compound according to Claim 1, in which the 5- and 6-substituents are in <u>trans</u> relationship.

18. A compound being a bicyclo [2,2,1] heptane or hept-2Z-ene, suitable for use in the preparation of a compound according to Claim 1, which is substituted at the 5-position by a 6-carboxyhex-2-enyl group or a modification thereof as defined herein, and at the 6-position by a group $-C(R_1)\begin{smallmatrix}\nearrow R_2\\ \searrow R_3\end{smallmatrix}$ in which R_1 represents hydrogen, an aliphatic hydrocarbon residue, an aromatic residue, or an aliphatic hydrocarbon residue substituted directly or through an oxygen or sulphur atom by an aromatic residue, R_2 represents hydrogen and R_3 represents a hydroxy group or R_2 and R_3 together represent a carbonyl group, with the proviso that both R_1 and R_2 may not be hydrogen and that when the substituent at the 5-position is a 6-carboxyhex-2-enyl group rather than a modification thereof then R_1 may not be hydrogen when R_2 and R_3 together represent a carbonyl group.

19. A compound according to Claim 18, in which the substituent at the 5-position is a 6-carboxyhex-2Z-enyl group or a 6-carboxyhexyl group or a derivative of such groups formed at the carboxy group thereof.

20. A compound according to Claim 18, in which the substituent at the 6-position is a group $-C(R_1)=O$ in which R_1 represents an aliphatic hydrocarbon residue, an aromatic residue or an aliphatic hydrocarbon residue substituted directly by an aromatic residue.

21. A compound according to Claim 18 wherein the substituent at the 5-position is a 6-carboxyhexyl group or a derivative thereof formed at the carboxy group and the substituent at the 6-position is a formyl group.

22. A pharmaceutical composition comprising a compound according to Claim 1 as an active ingredient thereof in combination with a physiologically acceptable diluent or carrier.

23. A compound according to Claim 1, in which the 5-substituent is oppositely disposed to the bridging methylene group.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 80/00001

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[3]

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

Int.Cl.^{3} C 07 C 177/00; A 61 K 31/557

II. FIELDS SEARCHED

Minimum Documentation Searched[4]

Classification System	Classification Symbols
Int.Cl.^{3}	C 07 C 177/00; A 61 K 31/557

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[14]

Category *	Citation of Document,[16] with indication, where appropriate, of the relevant passages[17]	Relevant to Claim No.[18]
A	FR, A, 2316926, published February 4, 1977 see claims, Sumitomo ------	1

* Special categories of cited documents:[15]

"A" document defining the general state of the art

"E" earlier document but published on or after the international filing date

"L" document cited for special reason other than those referred to in the other categories

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search[2] 27th February 1980	Date of Mailing of this International Search Report[2] 7th March 1980
International Searching Authority[1] European Patent Office	Signature of Authorized Officer[20] G.L.M. Kruydenberg

Form PCT/ISA/210 (second sheet) (October 1977)