# United States Patent [19]

**Anderson**

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[54] **ANTI-ATHEROSCLEROTIC INDOLIZINE DERIVATIVES**


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[51] **Int. Cl.**[4] ..... **A61K 31/435;** C07D 471/04

[52] **U.S. Cl.** ..... **514/299;** 546/112

[58] **Field of Search** ..... 546/112; 514/299



[56] **References Cited**

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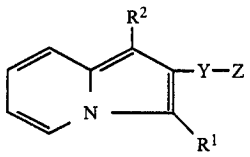
[57] **ABSTRACT**

7-(indolizin-2-yl)hept-6-enoic acids of the formula I:



I

wherein each of $R^1$ and $R^2$ is, independently, H, alkyl, cycloalkyl, aralkyl or aryl,

Y is $-CH=CH-$, or $-CH_2-CH_2-$; and

Z is $-CH(OH)-CH_2-CH(OH)-CH_2COOR^8$

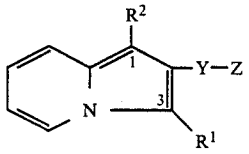
in which $R^8$ is H, an ester residue or cation; or the lactone thereof. The compounds are useful as hypocholesteremic agents.


**20 Claims, No Drawings**

# ANTI-ATHEROSCLEROTIC INDOLIZINE DERIVATIVES

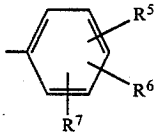
This invention pertains to organic compounds, and more particularly to 7-(indolizine-2-yl)-hept-6-enoic acid derivatives as well as to the use of such compounds and pharmaceutical compositions containing such compounds, as well as to intermediates and methods of preparation.

The final compounds involved in the invention may be conveniently represented by formula I:



I

wherein each of $R^1$ and $R^2$ is, independently:



(a)

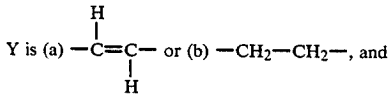
(b) hydrogen or a primary or secondary $C_{1-6}$alkyl not containing an asymmetric carbon atom, (c) $C_{3-6}$cycloalkyl or (d) phenyl—$(CH_2)_m$—,

wherein $R^5$ is hydrogen, $C_{1-3}$alkyl, n-butyl, i-butyl, t-butyl, $C_{1-3}$alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy;

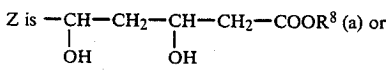
$R^6$ is hydrogen, $C_{1-3}$alkyl, $C_{1-3}$alkoxy, fluoro or chloro;

$R^7$ is hydrogen, $C_{1-2}$alkyl, $C_{1-2}$alkoxy, fluoro or chloro;

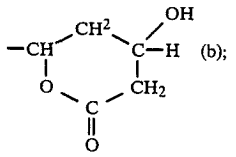
m is 1, 2 or 3;



Y is (a) —CH=CH— or (b) $-CH_2-CH_2-$, and



Z is —CH(OH)—$CH_2$—CH(OH)—$CH_2$—$COOR^8$ (a) or



(b);

in which $R^8$ is hydrogen, $R^9$ or M, wherein

$R^9$ is a physiologically acceptable and hydrolyzable ester group, and

M is a pharmaceutically acceptable cation

Compounds I may be viewed as consisting of various sub-classes depending upon the definition of their variable portions. Compounds I may be of the following subclasses depending on the nature of Z;

| Designation: | Z = | Nature |
|---|---|---|
| Compounds I1 | type (a); $R^8 = R^9$ | ester |
| Compounds I2 | type (a); $R^8$ = M | salt |
| Compounds I3 | type (a); $R^8$ = H, | free acid |
| Compounds I4 | type (b) | lactone |

A preferred type of Compounds I is designated I' where Y=(a) and one of $R^1$ and $R^2$ is H or alkyl, especially methyl or isopropyl, and the other is an aryl group i.e. (a), especially p-fluorophenyl, phenyl or 3,5-dimethylphenyl, and particularly p-fluorophenyl.

When $R^8$ is $R^9$, it is preferably ethyl, and when it is M, it is preferably sodium, potassium, magnesium or calcium, especially sodium.

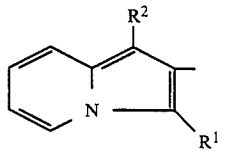
By the term "physiologically acceptable and hydrolyzable ester group" is meant a group which, together with the —COO— radical to which it is attached, forms an ester group which is physiologically acceptable and hydrolyzable under physiological conditions to yield a compound of Formula I wherein $R^8$ is hydrogen and an alcohol which itself is physiologically acceptable, i.e., non-toxic at the desired dosage level, and which, preferably, is free of centers of asymmetry. Examples of such groups are $C_{1-3}$alkyl, n-butyl, i-butyl, t-butyl and benzyl, collectively referred to as $R^{9'}$.

A particular sublcass of Compounds I is Compounds I1" in which $R^8$ is $R^{9''}$, i.e. $C_{1-4}$ primary alkyl, especially ethyl.

Compounds I may further be viewed as two subclasses depending on the nature of the group Y, i.e. Ia where Y=(a) and Ib where Y=(b), the former being preferred.

As is well known in the art, ester and salt forms of an organic acid are interconvertible. Hence, where an ester form (here I1) is prepared, it can then be saponified to its corresponding salt (I2) which can be neutralized to the free acid form (I3), which can be cyclized to the corresponding lactone (I4), and the reverse; all by adapting conventional processes. Accordingly, preparation of an ester I1 where $R^8$ is $R^{9''}$, i.e. I1", provides a compound of the invention, as well as a source of the corresponding other forms of Compounds I.

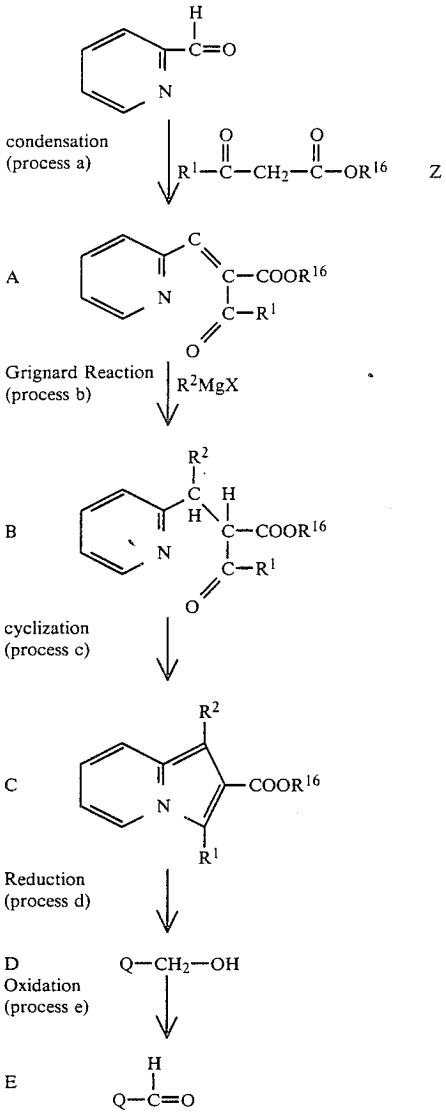
Compounds I1a" (i.e. Compounds I (in which Y=(a), Z=(a) and $R^8=R^{9''}$), are obtainable by a multi-step procedure which may conveniently be represented by Reaction Schemes A and B below, in which $R^1$, $R^2$ and $R^{9''}$ are as defined above, $R^{16}$ and $R^{17}$, are, independently, alkyl ($C_{1-3}$) preferably ethyl, $R^{20}$ is a primary or secondary $C_2$-$C_4$alkyl, eg ethyl; and $R^{21}$ is allyl or $C_1$-$C_4$alkyl, preferably not tertiary, e.g. methyl, X is Cl, Br or I, and Q has the structure:



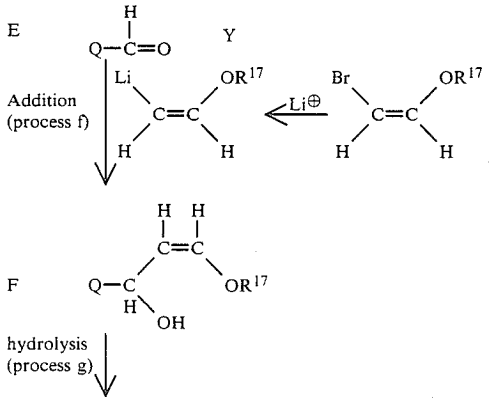
Q

in which $R^1$ and $R^2$ are as defined above.

REACTION SCHEME A




REACTION SCHEME B

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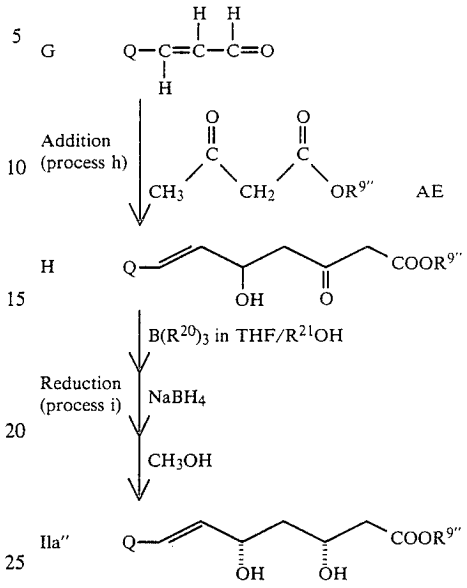
REACTION SCHEME B




Individually, each of the above described reactions is analogous to reactions, known in the art, except for process (i), and may be carried out in the conventional manner, unless indicated otherwise.

The parameters applicable to the processes illustrated in the Reaction Schemes, above, are listed in the following tables, in which general parameters are described with preferences as examples. In processes in which a medium is employed, it is understood that the medium is an inert solvent under the reaction conditions and is essentially anhydrous, i.e. moisture-free, if dry, i.e. essentially anhydrous conditions are called for. Where anhydrous conditions are called for, it is preferred that such reaction be carried out in an inert atmosphere eg under dry nitrogen gas.

In the tables, Q indicates an alkali metal salt usually used in situ, and [ ]indicates an adduct or complex reaction product which is reacted in a subsequent quenching step, usually quenched to hydrolyze or decompose it. Where a quenching step is employed, water is used, but often as an aqueous solution, e.g. saturated aqueous $NH_4Cl$. LAH=lithium aluminum hydride; ether=diethyl ether; RT=20° to 30° C., THF=tetrahydrofuran and PTS=p-toluenesulfonic acid. All temperatures are in degrees centigrade; these abbreviations etc., also applying to the Examples hereinafter presented.

Process (i) is novel and is not claimed as part of this invention. In an alternative method of carrying out process (i), in place of a trialkyl borane reagent there may be used an equivalent amount of a monoalkoxy dialkyl borane of the formula Gk:

$$R^{22}O—B—(R^{20})_2 \qquad \text{Gk}$$

in which $R^{20}$ and $R^{21}$ are defined hereinafter in the tables, and $R^{22}$ is allyl or a lower alkyl having from 1 to 4 carbon atoms, preferably not tertiary. $R^{20}$, $R^{21}$ and $R^{22}$ may be the same, but need not be. Preparation of Compounds Gk are described by Koster et al, Ann., 1975, 352. $R^{21}$ and $R^{22}$ are preferably methyl.

TABLE A

| | |
|---|---|
| Process (a): | Condensation |
| Reactant(s): | 2-pyridyl-CHO + Z → A |
| Medium: | Neat |
| Temperature: | 20° to 80° C., eg RT, then 80° C. |
| Conditions: | Catalytic amount of piperidine; dry. |
| Process (b): | Grignard Reaction |
| Reactant(s): | (1) A + $R^2MgX$ → [ ];<br>(2) quench, eg, aq. $NH_4Cl$ → B. |
| Medium: | Cyclic ether, eg THF, with Grignard reagent in ether. |
| Temperature: | (1) −70 to RT (add Cu(1)I at about 0°). |
| Conditions: | Dry, cat. amt. of Cu(1)I. |
| Process (c): | Cyclization |
| Reactant(s): | (1) B + Acetic Acid Anhydride; → [ ];<br>(2) quench (water) → C |
| Medium: | Excess AAA. |
| Temperature: | Reflux. |
| Conditions: | — |
| Process (d): | Ester Reduction |
| Reactant(s): | (1) C + LAH → [ ];<br>(2) Destroy excess LAH with ethyl acetate, then quench with ice-water → D. |
| Medium: | THF |
| Temperature: | (1) −5° C. to 30° C., eg add LAH at 0° C. to raise to RT;<br>(2) Cold. eg ice-water bath. |
| Conditions: | (1) dry; (2) add ethylacetate cautiously. |
| Process (e): | Oxidation to aldehyde |
| Reactant(s): | D + $MnO_2$ → E |
| Medium: | Inert hydrocarbon, eg toluene. |
| Temperature: | 20 to 140°, eg reflux conditions. |
| Conditions: | Dry |
| Process (f): | Addition of olefinic unit |
| Reactant(s): | (1) BrCH═CH—$OR^{17}$, eg $R^{17}$ = ethyl, + $Li^{\oplus}$ source, eg t-butyl lithium → Y<br>(2) Y + E → [ ].<br>(3) [ ] + quench, eg ice-water or sat. aq. $NH_4Cl$, → F |
| Medium: | (1) Cyclic ether, eg THF; (1) = (2). |
| Temperature: | (1) −40 to −100° C., eg about −70°;<br>(1) = (2); (3) 0° C. to RT. |
| Conditions: | Essentially anhydrous for (1) + (2). |
| Process (g): | Hydrolysis |
| Reactant(s): | F + aq. PTS → G |
| Medium: | Cyclic ether, eg THF + water in ratio of about 4:1. |
| Temperature: | RT |
| Conditions: | — |
| Process (h): | Addition via dianion (3 stages) |
| Reactant(s): | (1) AE, eg ethyl acetate, + 2 equivalents of alkali cation, eg 2 LDA → Q.<br>(2) Q + G → [ ].<br>(3) [ ] + quench, eg ice-water or saturated aqueous $NH_4Cl$ → H. |
| Medium: | (1) Cyclic ether, eg THF.<br>(1) = (2) = (3). |
| Temperature: | (1) −60 to +5°, eg 0 to +5°.<br>(2) −80° to −20°, eg −75° to −60°.<br>(3) 0° to R.T. |
| Conditions: | Dry for (1) + (2). |
| Process (i): | Reduction (3 stages) |
| Reactant(s): | (1) H + $B(R^{20})_3$ eg $R^{20}$ = ethyl, in a ratio of about 1:1.02 to 1.3 → [ ].<br>(2) $NaBH_4$ + [ ] → [ ]'.<br>(3) [ ]' + $H^{\oplus}$, eg acetic acid, → I1a'' |
| Medium: | (1) THF/$R^{21}$OH, eg, $R^{21}$ = methyl; ratio = 3 to 6:1, eg 3–4:1.<br>(1) = (2) = (3). |
| Temperature: | (1) R.T.<br>(2) −100 to −40°, eg −75°.<br>(3) −100 to −40°, eg −75°, then to R.T. |
| Conditions: | Dry for (1) + (2).<br>Optionally, air may be bubbled through reaction mixture in (1). |

Analogs of Compounds I1a'' in which Y is of type (b) i.e. Compounds I1b'' are conveniently obtained by a two-step procedure, by first saturating the olefinic unit of a corresponding compound H (process j) to yield a saturated analog of a compound H, i.e. a compound Hb, and then reducing such compound in a manner analogous to process (i).

Process (j) may be carried out in the conventional manner for hydrogenating an ethylenically unsaturated bond, under conditions that do not alter the remainder of the compounds; for example at about 20° to 40° C., e.g. R.T. under a pressure of about 40 to 50 p.s.i. of hydrogen gas in the presence of a hydrogenation catalyst e.g., 5% palladium on charcoal or 5% rhodium on charcoal, in an inert medium, e.g. a lower alkanol, such as ethanol. alternatively a compound I1a'' can be reduced by the procedure of process (j) to obtain its corresponding saturated analog (a compound I1b''). As described above, such esters can be converted by known means to their corresponding free acid, salt and lactone forms.

The products described herein may be recovered and refined, where such is desired, by conventional means, such as by crystallization, distillation or chromatographic techniques such as column or thin layer chromatography, (TLC) e.g., silica gel column chromatography. Where appropriate, intermediates can be employed directly in a subsequent reaction.

Reagents and starting materials employed in the above-described processes, e.g. 2-pyridine carboxaldehyde and Y, Z, AE and $B(R^{20})_3$, are either known and may be obtained as described in the literature, or where not known may be prepared by methods reported in the literature for the preparation of known analogues. Some are commercially available.

## UTILITY STATEMENT

The compounds of Formula I are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis, and, therefore, they are inhibitors of cholesterol biosynthesis. Consequently, they are useful for lowering the blood cholesterol level in animals, e.g., mammals, especially larger primates such as humans, and, therefore, as hypolipoproteinemic and anti-atherosclerotic agents. The biological activity of the compounds of Formula I may be demonstrated in the following two tests:

Test A. In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition:

This test is known and is carried out as described on pages 59–60 of application Ser. No. 06/741,903 (filed June 6, 1985) and on page 30 of World (PCT) Published Patent Application No. 84/02131 both of which are hereby incorporated by reference as if set forth herein in their entirety. The concentration of the test substance (compound of Formula I) in the assay system is 0.0005–2,000 μmolar. The obtained $IC_{50}$ is the concentration of the test substance in the assay system observed or calculated to produce a 50% inhibition of HMG-CoA reductase activity.

Test B. In Vivo Cholesterol Biosynthesis Inhibition Test:

This test is also known and is carried out as described on pages 60–61 of said application Ser. No. 06/741,903 and on page 33 of World (PCT) Published Patent Application No. 84/02131, both of which are hereby incorporated by reference as if set forth herein in their entirety. In this test the rats are orally administered the test substance (compound of Formula I) at a dose of 0.025–200 mg/kg. body weight. The obtained $ED_{50}$ is the dose of the test substance observed or calculated to

produce a 50% inhibition of 3 β-hydroxysterol synthesis.

In Test A, tested compounds of Formula I had $IC_{50}$'s of about 0.006 to over 10 μmolar whereas that of Compactin was 1.01 μmolar and that of Mevinolin was 0.14 μmolar. The preferred compound of this application, that of Example 2, had an $IC_{50}$ of 0.011 μmolar. In Test B, the compound of Example 1 had an $ED_{50}$ of 0.05 mg/kg. whereas that of Compactin was 3.5 mg/kg. and that of Mevinolin was 0.41 mg/kg.

Since they inhibit cholesterol biosynthesis, the compounds of Formula I (including those of each subgroup thereof) are useful for lowering the blood cholesterol level in animals, eg., mammals, especially larger primates, in particular humans, and, therefore, as hypolipoproteinemic and anti-atherosclerotic agents.

The precise dosage of the compound of Formula I to be employed for inhibitng cholesterol biosynthesis depends upon several factors including the host, the nature and the severity of the condition being treated, and the mode of administration and the particular active substance (compound of Formula I) employed. However, in general, suitable oral daily dosages of the compounds of Formula I for the satisfactory inhibition or reduction of cholesterol biosynthesis (i.e., the satisfactory reduction of blood cholesterol level and satisfactory treatment of hyperlipoproteinemia and atherosclerosis) are indicated by the test data to be 0.025–100 mg/kg. body weight, e.g., 0.025–5 mg/kg. body weight for the more active compounds. For most larger primates such as humans, a suitable oral daily dosage is indicated to be 0.1–2,000 mg., e.g., 2–140 mg. for the more active compounds. The daily dosage of the compound of Example 2, is indicated to be from about 2 to 140 mg., preferably from about 2 to 20 mg., for most larger primates such as humans. For administration by injection, a dosage somewhat lower than would be used for oral administration of the same active substance to the same host having the same condition is usually employed. However, the above dosages are also typically used for I.V. administration.

The daily dosage may be administered in a single dose but more typically is administered in two to four equal portions, typical doses being 0.5 to 1000 mg. Often, a small dosage is administered initially, and the dosage is gradually increased until the optimal dosage for the host under treatment is determined.

A typical dosage unit for oral administration may contain 0.5 to 500 e.g. 0.5 to 10 mg of a compound of Formula I.

The compounds of Formula I may be formulated into conventional pharmaceutical compositions and administered by any conventional mode of administration, in particular enterally, e.g., in the form of capsules or tablets, or parenterally, e.g., in the form of sterile injectable solutions or suspensions. The pharmaceutical compositions comprise a compound of Formula I and at least one pharmaceutically acceptable solid or liquid carrier (or diluent). They may be formulated in conventional manner. The compounds of each subgroup thereof may likewise be formulated into such pharmaceutical compositions and administered by such routes.

The compounds of Formula I (including those of each subgroup thereof) may be formulated into such pharmaceutical compositions containing an amount of the active substance that is effective for inhibiting cholesterol biosynthesis in unit dosage form and such compositions comprising at least one solid pharmaceutically acceptable carrier.

A representative formulation suitable for encapsulation in a hard gelatin capsule by conventional techniques is:

Compound of Formula I, e.g., the compound of

| Compound of Formula I, e.g., the compound of | |
|---|---|
| Example 2 | 1 mg. |
| Corn starch | 248 mg. |
| Magnesium stearate | 1 mg. |

As is self-evident to those in the art, each compound of formula I (and every sub-scope and species thereof) has at least two centers of asymmetry (e.g. the two carbon atoms bearing the hydroxy groups in the structure when Z=a) and the carbon atom bearing the hydroxy group and the carbon atom having the free valence in the structure when Z=b), and these lead (e.g. with two centers) to four stereoisomeric forms (enantiomers) of each compound (two racemates or pairs of diastereoisomers). The preferred compounds have only two such centers of asymmetry and these four stereoisomers may be designated as the R,R; R,S; S,R; and S,S enantiomers, all four stereoisomers being within the scope of this invention.

The preferred stereoisomers of the compounds of formula I having only two centers of asymmetry wherein Y is a) and Z is a) are the 3R,5S and 3R,5R isomers and the racemate of which each is a constituent, i.e., the 3R,5S-3S,5R (erythro) and 3R,5R-3S,5S (threo) racemates, with the 3R,5S isomer and the racemate of which it is a constituent being more preferred and the 3R,5S isomer being most preferred.

The preferred stereoisomers of the compounds of formula I having only two centers of asymmetry wherein Y is (b) and Z is (a) are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, i.e., the 3R,5R-3S,5S (erythro) and 3R,5S-3S,5R (threo) racemates, with the 3R,5R isomer and the racemate of which it is a constituent being more preferred and the 3R,5R isomer being most preferred.

The preferred stereoisomers of the compounds of formula I having only two centers of asymmetry wherein Y is (a) and Z is (b) are the 4R,6S and 4R,6R isomers and the racemate of which each is a constituent, i.e., the 4R,6S-4S,6R (trans lactone) and 4R,6R-4S,6S (cis lactone) racemates, with the 4R,6S isomer and the racemate of which it is a constituent being more preferred and the 4R,6S isomer being most preferred.

The preferred stereoisomers of the compounds of formula I having only two centers of asymmetry wherein Y is (b) and Z is (b) are the 4R,6R and 4R,6S isomers and the racemate of which each is a constituent, i.e., the 4R,6R-4S,6S (trans lactone) and 4R,6S-4S,6R (cis lactone) racemates, with the 4R,6R isomer and the racemate of which it is a constituent being more preferred and the 4R,6R isomer being most preferred.

The preferences set forth in the preceding four paragraphs also apply to the compounds of formula I having more than two centers of asymmetry and represent the preferred configurations of the indicated positions.

Compounds I having one or more of the following characteristics are preferred:

(a) Y=(a);

(b) Z=(a) ;

(c) when Z=a, $R^8$=M, especially sodium;

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