NOVEL 2-SACCHARINYLMETHYL ARYL CARBOXYLATES USEFUL AS PROTEOLYTIC ENZYME INHIBITORS AND COMPOSITIONS AND METHOD OF USE THEREOF

This invention relates to novel 2-saccharinylmethylaryl carboxylates, which inhibit the enzymatic activity of proteolytic enzymes, to compositions containing the same, to the method of use thereof in the treatment of degenerative diseases and to processes for their preparation.

The inhibition of proteolytic enzymes by nontoxic reagents is useful in the treatment of degenerative disorders, such as emphysema, rheumatoid arthritis and pancreatitis, in which proteolysis is a substantive element.

Protease inhibitors are widely utilized in biomedical research. Serine proteases are the most widely distributed class of proteolytic enzymes. Some serine proteases are characterized as chymotrypsin-like or elastase-like based upon their substrate specificity.

Chymotrypsin and chymotrypsin-like enzymes normally cleave peptide bonds in proteins at a site at which the amino acid residue on the carboxyl side is typically Trp, Tyr, Phe, Met, Leu or another amino acid residue which contains aromatic or large alkyl side chains.

Elastase and elastase-like enzymes normally cleave peptide bonds at a site at which the amino acid residue on the carboxyl side of the bond is typically Ala, Val, Ser, Leu or other similar, smaller amino acids.

Both chymotrypsin-like and elastase-like enzymes are found in leukocytes, mast cells and pancreatic juice in higher organisms, and are secreted by many types of bacteria, yeast and parasites.

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Japanese Patent Publication 7200419 discloses a number of 2-saccharinylmethylbenzoates, including 2-saccharinylmethyl benzoate per se and 2-saccharinylmethyl 2,4-dichlorobenzoate and 4-nitrobenzoate. The compounds are said to have strong activity against rice blast, rice sheath blight, rice helminthosporium leaf spot and rice bacterial leaf blight disease.

Sunkel et al., J. Med. Chem., 31, 1886-1890 (1988) disclose a series of 2-saccharinyl-lower-alkyl-1,4-dihydropyridine-3-carboxylates having platelet aggregation inhibitory and anti-thrombotic activities.

Chen U.S. Patent 4,263,393 discloses various 2-aroylmethylsaccharins useful as photographic elements and film units.

Mulvey et al. U.S. Patent 4,195,023 discloses R_1-2-R_2CO-1,2-benzisothiazol-3-ones, where R_1 is halogen, alkoxy, alkylamino, dialkylamino, alkoxycarbonyl, amino, nitro or hydrogen in the benzenoid ring and R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, halophenyl, heteroaryl or substituted heteroaryl, and R_1-2-A-CO saccharins, where R_1 has the same meanings as the benzenoid ring substituents in the 1,2-benzisothiazol-3-ones and A is alkyl, alkenyl, alkynyl, cycloalkyl, fluorophenyl, heteroaryl or substituted-heteroaryl. The compounds are said to have elastase inhibitory activity and to be useful in the treatment of emphysema.

Zimmerman et al., J. Biol. Chem., 225(20), 9848-9851 (1980) disclose N-acylsaccharins, where the acyl group is furoyl, thenoyl, benzoyl, cyclopropanoyl, ethylbutyryl and acryloyl, having serine protease inhibitory activity.

Japanese Patent Publication 73/35457 discloses 4-methylphenyl 2-saccharinyl-carboxylate which is said to have bactericidal and fungicidal activities.

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Several classes of compounds are known to be serine protease inhibitors. For example Powers in U.S. Patent 4,659,855 discloses arylsulfonyl fluoride derivatives useful as elastase inhibitors. Doherty et al. U.S. Patents 4,547,371 and 4,623,645 disclose cephalosporin sulfones and sulfoxides, respectively, which are stated to be potent elastase inhibitors useful in the treatment of inflammatory conditions, especially arthritis and emphysema.

Teshima et al., J. Biol. Chem., 257(9), 5085-5091 (1982) report the results of studies on serine proteases (human leukocyte elastase, porcine pancreatic elastase, cathepsin G and bovine chymotrypsin A_α) with 4-nitrophenylesters and thioesters of N-tri-fluoroacetylanthranilates, 2-substituted-4H-3,1-benzoxazin-4-ones, 2-substituted-4-quinazolinones and 2-substituted-4-chloroquinazolines.

Cha, Biochem. Pharmacol., 24, 2177-2185 (1975) discusses kinetic approaches to the study of the binding of inhibitors to macromolecules, such as enzymes, and methods for determination of such parameters as the inhibition constants, reaction rates and bound and unbound enzyme concentrations.

Jones et al., U.S. Patent 4,276,298 discloses 2-R-1,2-benzisothiazolinone-1,1-dioxides, where R is phenyl substituted by fluoro, dinitro, trifluoromethyl, cyano, alkoxycarbonyl, alkylcarbonyl, carboxyl, carbamoyl, alkylacylamino, alkylsulfonyl, N,N-dialkyl-sulfamoyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfonyl and trifluoromethylsulfinyl, or pyridyl substituted the same as R when R is phenyl except that pyridyl may also be mononitro substituted. The compounds are said to have protease enzyme inhibitory activity, especially elastase inhibitory activity, and to be useful in the treatment of

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emphysema, rheumatoid arthritis and other inflammatory diseases.

Powers, Biochem., 24, 2048-2058 (1985) discloses studies of the inhibitions of four chymotrypsin-like enzymes, cathepsin G, rat mast cell proteases I and II, human skin chymase and chymotrypsin A_α, by N-furoylsaccharin and N-(2,4-dicyanophenyl)saccharin.

Svoboda et al., Coll. Czech. Chem. Commun., 51, 1133-1139 (1986) disclose the preparation of 4-hydroxy-2H-1,2-benzothiazine-3-carboxylates by intramolecular Dieckmann condensation of 2H-1,2-benzisothiazol-3-one-2-acetate-1,1-dioxide esters.

Reczek et al., U.S. Patents 4,350,752 and 4,363,865 and Vanmeter et al. U.S. Patent 4,410,618 relate to photographic reagents (Reczek 4,350,752 and Vanmeter et al.) and photographic dyes (Reczek 4,363,865) and disclose various 2-substituted-saccharins useful for such applications, for example photographic reagents bound through a heteroatom to an imidomethyl blocking group (Reczek 4,350,752), carrier-diffusible photographic dyes bound to the nitrogen atom of an imide through a 1,1-alkylene group (Reczek 4,363,865) and N-acylmethylimides which are described as blocked photographic reagents and which have a residue of an organic photographic reagent containing a hetero atom through which it is bound to the blocking group (Vanmeter).

Freed U.S. Patent 3,314,960 discloses 2-(1,1,3-trioxo-1,2-benzisothiazol-2-yl)glutarimides which are stated to be useful as sedatives.

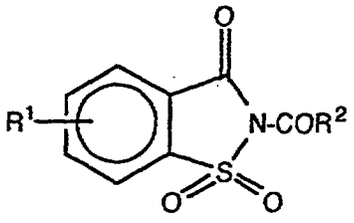
2-Chloromethylsaccharin is disclosed in French Patent 1,451,417 as an intermediate for the preparation of N-methylsaccharin d,l-trans-chrysanthemate, useful

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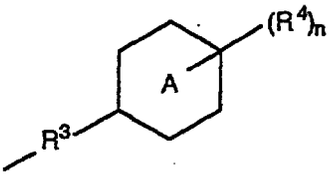


as an insecticide, and Lo U.S. Patent 3,002,884 discloses 2-chloro, 2-bromo and 2-iodomethylsaccharins, useful as fungicidal agents.

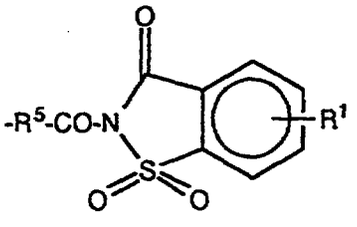
Ladislas et al., European Patent Application 446047A1 disclose compounds of the formula:



where R^1 is a hydrogen atom or a C_1-C_5 alkyl or alkoxy group, and R^2 is a monovalent C_8-C_{20} alkyl or C_9-C_{20} alkenyl group, optionally substituted with OH or COOH group, or R^2 is a group with the formula:



where R^3 is a divalent straight or branched C_2-C_6 saturated or ethylenically unsaturated aliphatic group;  is an aromatic nucleus; R^4 is OH, a C_1-C_4 alkyl or a C_1-C_4 alkoxy group, n is zero or an integer in the range of 1-5, and when n>1, the R^4 groups can be different, or else R^2 is a group of the formula:



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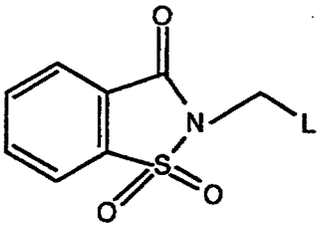
where R^1 is the same as above, and R^5 is a divalent straight or branched C_8-C_{20} saturated or ethylenically unsaturated group. The compounds are said to exhibit elastase inhibitory activity.

Yoon et al., J. Korean Agricultural Chemical Society 1986, 29(2), 164-174, disclose N-methyl, N-alkyl ester, N-benzyl, N-benzoyl, N-benzoyloxymethyl, N-benzyloxymethyl, N-(p-nitrobenzoyloxy)methyl and N-(p-nitrophenyloxy)methyl saccharin derivatives. The compounds are said to be useful as antifungal agents.

Dunlap et al., PCT Application WO 90/13549 disclose a series of 2-substituted saccharin derivatives useful as proteolytic enzyme inhibitors. Example 1 is identified as 2-acetoxymethyl-4-methylsaccharin.

Sunkel et al., European Patent Application 253092 disclose 2-saccharinyl-lower-alkyl-1,4-dihydro-pyridine-3-carboxylates having platelet aggregation inhibitory and antithrombotic activities. This reference corresponds substantially to Sunkel et al. J. Med. Chem. 31, 1886-1890 (1988) as hereinbefore described.

Groutas et al., Bioorganic and Medicinal Chemistry Letters 1992, 2(2), 175-180, disclose compounds of the formula:



wherein L is ibuprofen (compound IIa) Cbz-L-leu (compound IIb) or -COOBzl (compound IIC). The compounds are said to be useful as human leukocyte elastase (HLE) inhibitors.

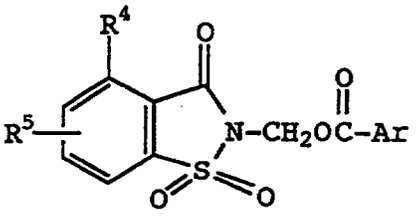
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The present invention relates to 4-R^4-R^5-2-saccharinylmethyl aryl carboxylates which have protease enzyme inhibitory activity and which are useful in the treatment of degenerative diseases.

The invention further relates to compositions for the treatment of degenerative diseases which comprise a pharmaceutical carrier and an effective proteolytic enzyme inhibiting amount of a 4-R^4-R^5-2-saccharinylmethyl aryl carboxylate.

The invention further relates to the use of 2-saccharinylmethyl aryl carboxylates in the treatment of degenerative diseases which comprises administering to a patient in need of such treatment a medicament containing an effective proteolytic enzyme inhibiting amount of a 4-R^4-R^5-2-saccharinylmethyl aryl carboxylate.

More specifically this invention relates to 4-R^4-R^5-2-saccharinylmethyl aryl carboxylates having the formula:



I

wherein:

1) Ar is halophenyl, halonaphthyl or haloanthryl substituted by from one to three, the same or different, members of the group consisting of -O-(alkylene)-1-lower-alkyl-4-piperidinyl, and -O-(alkylene)-1-lower-alkyl-2-or 3-pyrrolidinyl;

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R^4 is hydrogen, halogen, lower-alkyl, perfluorolower-alkyl, perchlorolower-alkyl, polyfluoro-lower-alkyl, polychlorolower-alkyl, lower-alkenyl, lower-alkynyl, cyano, amino, lower-alkylamino, dilower-alkylamino, lower-alkoxy, benzyloxy, lower-alkoxy-carbonyl, phenyl or carboxamido; and

R^5 is hydrogen or from one to two the same or different substituents in any of the 5-, 6- or 7-positions selected from halogen, cyano, nitro, N=B, 1-lower-alkyl-2-pyrrolyl, lower-alkyl-sulfonylamino, polyfluorolower-alkyl-sulfonylamino, polychlorolower-alkylsulfonylamino, aminosulfonyl, lower-alkyl, poly-fluorolower-alkyl, polychlorolower-alkyl, cycloalkyl, lower-alkoxy, hydroxy, carboxy, carboxamido, hydroxy-lower-alkyl, methylenedioxy, cycloalkyloxy, formyl, aminomethyl, lower-alkyl-sulfonyl, polyfluorolower-alkylsulfonyl, polychloro-lower-alkylsulfonyl, lower-alkylsulfonylaminosulfonyl, lower-alkoxypoly-lower-alkyleneoxy, benzyloxypolylower-alkyleneoxy, hydroxy-poly-lower-alkyleneoxy, benzyloxy-lower-alkoxy, hydroxylower-alkoxy, polyhydroxylower-alkoxy or acetal or ketal thereof or said hydroxy groups of polyhydroxy-lower-alkoxy substituted by benzyl; poly(lower-alkoxy)-lower-alkoxy, -SR, -SOR, $-SO_2R$, -OCOR, -O-(alkylene)-COOR, -O-(alkylene)-COOH, -O-(alkylene)-N=B, $-O-C(R')_2COOH$, $-O-C(R')_2-COOR$, $-O-C(X')_2COOH$, $-O-C(X')_2COOR$, $-O-(CH_2)_nOC(O)(CH_2)_n-N=B$, $-O-(CH_2)_n-O-(CH_2)_nOC(O)(CH_2)_n-N=B$, $-O-(CH_2O)_m-A$, $-O-(CH_2)_n-(5-((CH_2)_n-N=B)-2-furanyl)$, $-O-(CH_2)_n-(5-((CH_2)_n-N=B)-2-thienyl)$, $-O-(CH_2)_n-(5-((CH_2)_n-N=B)-1-R-2-pyrrolyl)$, $-O-(CH_2)_m-C(O)-N=B''$, $-O-(CH_2)_n-=-(CH_2)_n-N=B''$, $-O-(CH_2)_n-=-(CH_2)_n-N=B''$, aminosulfonyloxy, or dilower-alkylaminosulfonyloxy, wherein R is lower-alkyl, phenyl, benzyl, 1,1-diphenylmethyl, or naphthyl, or

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phenyl or napthyl substituted by from one to two substituents selected from lower-alkyl, lower-alkoxy or halogen; where N=B in each instance is amino, lower-alkylamino, dilower-alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl, carboxy-lower-alkylamino or -N-lower-alkyl-(alkylene-N(alkyl)$_2$; each R' group is independently hydrogen, or lower-alkyl; X' is chlorine or fluorine; n is an integer from one to four; m is an integer from zero to four; A is an azetidinyl, pyrrolidinyl, or piperidinyl ring attached through any available carbon atom, or said ring substituted on nitrogen by an R substitutent wherein R is as defined above; N=B" is amino, lower-alkylamino, dilower-alkylamino, dibenzylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 4-tert-butoxy-carbonyl-1-piperazinyl, 1-imidazolyl, or -NR"(alkylene)-N(alkyl)$_2$ wherein R" is hydrogen or lower-alkyl; and N=B"' is amino, lower-alkylamino, dilower-alkylamino, dibenzylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl, or -NR"(alkylene)-N(alkyl)$_2$ wherein R" is hydrogen or lower-alkyl;

or R^5 is a 5- or 6-membered saturated ring fused to the saccharin at the 5,6 or 6,7 positions, said ring containing two heteroatoms chosen from the group consisting of nitrogen, oxygen and sulfur or a methylated derivative of said ring;

or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof; or

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2) Ar is phenyl, naphthyl or anthryl or such groups substituted by from one to three, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, perchlorolower-alkyl, lower-alkoxy, halogen, nitro, cyano, carboxy, PO(lower-alkoxy)$_2$, amino, lower-alkylamino, dilower-alkylamino, lower-alkanoylamino, lower-alkoxycarbonyl, hydroxy, benzyloxy, carboxy-lower-alkoxy, -SO_2-N=B, -CO-N=B, -(alkylene)-N=B, -COO(alkylene)-N=B, -NH(alkylene)-N=B; -N(lower-alkyl)-(alkylene)-N=B or -O-(alkylene)-N=B, where N=B is as defined above;

R^4 is as defined above; and

R^5 is from one to two, the same or different substituents in any of the 5-, 6-, or 7-positions selected from benzyloxypoly-lower-alkyleneoxy, hydroxy-poly-lower-alkyleneoxy, benzyloxylower-alkoxy, poly-hydroxylower-alkoxy in which the hydroxy groups are substituted by benzyl; -O-(alkylene)-COOH, -O-C(R')$_2$COOH, -O-C(R')$_2$COOR, -O-C(X')$_2$COOH, -O-C(X')$_2$COOR, -O-$(CH_2)_n$OC(O)$(CH_2)_n$-N=B, -O-$(CH_2)_n$-O-$(CH_2)_n$OC(O)$(CH_2)_n$-N=B, -O-$(CH_2O)_m$-A, -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-2-furanyl), -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-2-thienyl), -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-1-R-2-pyrrolyl, -O-$(CH_2)_m$-C(O)-N=B", -O-$(CH_2)_n$-≡-$(CH_2)_n$-N=B"', -O-$(CH_2)_n$-=-$(CH_2)_n$-N=B"', aminosulfonyloxy, or dilower-alkylaminosulfonyloxy, wherein R, N=B, R', X', n, m, A, N=B" and N=B"' are as defined above;

or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof.

Preferred compounds of formula I above in 1) are those wherein Ar is 2,6-dichloro-3-[O-(alkylene)-1-lower-alkyl-2-pyrrolidinyl]phenyl or 2,6-dichloro-3-[O-(alkylene)-1-lower-alkyl-3-pyrrolidinyl]phenyl and especially 2,6-dichloro-3-[O-(alkylene)-1-lower-alkyl-

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4-piperidinyl]phenyl, in particular when R^4 is lower-alkyl and R^5 is lower-alkoxy.

Particularly preferred compounds of those above are those wherein Ar is 2,6-dichloro-3-[O-(CH_2CH_2)-1-methyl-4-piperidinyl]phenyl, R^4 is lower-alkyl and R^5 is lower-alkoxy, especially 4-isopropyl-6-methoxy-2-saccharinylmethyl 2,6-dichloro-3-[2-(1-methyl-4-piperidinyl)ethoxy]benzoate.

Preferred compounds of formula I in 2) are those wherein:

Ar is phenyl, naphthyl or anthryl or such groups substituted by from one to three, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, lower-alkoxy, halogen, nitro, -PO(lower-alkoxy)$_2$, lower-alkanoylamino, hydroxy, benzyloxy, carboxy-lower-alkoxy, -SO_2-N=B or -O-(alkylene)-N=B, where N=B in this instance is dilower-alkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, carboxylower-alkylamino or -N-lower-alkyl-(alkylene)-N(alkyl)$_2$; and

R^4 is hydrogen, primary or secondary lower-alkyl, lower-alkoxy or phenyl.

Particularly preferred compounds of this group are those wherein:

Ar is phenyl or phenyl substituted by from one to three, the same or different, members selected from the group consisting of lower-alkyl, lower-alkoxy, halogen, hydroxy, benzyloxy, carboxy-lower-alkoxy, -SO_2-N=B or -O-(alkylene)-N=B, where N=B is as last defined;

R^4 is primary or secondary lower-alkyl or lower-alkoxy; and

R^5 is hydroxypoly-lower-alkyleneoxy, benzyl-oxylower-alkoxy, polyhydroxylower-alkoxy in which the hydroxy groups are substituted by benzyl;

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-O-(alkylene)-COOH, -O-C(R')$_2$COOH, -O-C(R')$_2$COOR, -O-(CH$_2$)$_n$OC(O)(CH$_2$)$_n$-N=B, -O-(CH$_2$O)$_m$-A, -O-(CH$_2$)$_n$-(5-((CH$_2$)$_n$-N=B)-2-furanyl), -O-(CH$_2$)$_m$-C(O)-N=B", -O-(CH$_2$)$_n$-≡-(CH$_2$)$_n$-N=B"', or dilower-alkylaminosulfonyloxy, wherein N=B is as last defined and R', n, m, A, N=B" and N=B"' are as defined above.

Most particularly preferred compounds of Formula I within this latter group are those wherein:

R^5 is one substituent in the 6-position selected from hydroxypoly-lower-alkyleneoxy, benzyloxy-lower-alkoxy, polyhydroxylower-alkoxy in which the hydroxy groups are substituent by benzyl; -O-(alkylene)-COOH, -O-C(R')$_2$COOH, -O-C(R')$_2$COOR, -O-(CH$_2$)$_n$OC(O)(CH$_2$)$_n$-N=B, -O-(CH$_2$O)$_m$-A, -O-(CH$_2$)$_n$-(5-((CH$_2$)$_n$-N=B)-2-furanyl), -O-(CH$_2$)$_m$-C(O)-N=B", -O-(CH$_2$)$_n$-≡-(CH$_2$)$_n$-N=B"', or dilower-alkylaminosulfonyloxy, wherein R is benzyl; N=B is dilower-alkylamino; R' is hydrogen; n and m are as defined above; A is 3-azetidinyl ring or a 1-(1,1-diphenylmethyl)-3-azetidinyl ring; N=B" is dilower-alkylamino, dibenzylamino, 4-lower-alkyl-1-piperazinyl, 4-tert-butoxycarbonyl-1-piperazinyl, or -NR"(alkylene)-N(alkyl)$_2$ wherein R" is hydrogen or lower-alkyl; and N=B"' is dilower-alkylamino, especially when

Ar is 2,6-dichlorophenyl and

R^4 is secondary lower-alkyl or lower-alkoxy.

A particularly preferred compound within this group is 4-isopropyl-6-[1-(carboxy)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate.

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It should be understood that the compounds having the general structural formula I are usually named in the chemical literature as 1,2-benzisothiazol-3(2H)-one 1,1-dioxides. However for the sake of brevity, such compounds are frequently named as saccharin derivatives, and that nomenclature will be used hereinafter in describing the compounds of the invention and their biological properties.

As used herein the terms lower-alkyl, lower-alkoxy and lower-alkane mean monovalent aliphatic radicals, including branched chain radicals, of from one to ten carbon atoms. Thus the lower-alkyl (or lower-alkane) moiety of such groups include, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl, neopentyl, n-hexyl, 1-methylpentyl, 3-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 2-hexyl, 3-hexyl, 1,1,3,3-tetramethylpentyl, 1,1-dimethyloctyl and the like.

As used herein the term halogen (or halo) or halide means fluorine, chlorine, bromine or iodine.

As used herein the terms lower-alkenyl and lower-alkynyl mean monovalent, unsaturated radicals, including branched chain radicals, of from two to ten carbon atoms and thus include 1-ethenyl, 1-(2-propenyl), 1-(2-butenyl), 1-(1-methyl-2-propenyl), 1-(4-methyl-2-pentenyl), 4,4,6-trimethyl-2-heptenyl, 1-ethynyl, 1-(2-propynyl), 1-(2-butynyl), 1-(1-methyl-2-propynyl), 1-(4-methyl-2-pentynyl), and the like.

As used herein, the term alkylene means divalent, saturated radicals, including branched chain radicals, of from two to ten carbon atoms and having their free valences on different carbon atoms and thus includes 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1-methyl-1,2-ethylene, 1,8-octylene and the like.

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As used herein cycloalkyl means C_3 through C_7 saturated monocyclic hydrocarbon residues and thus includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

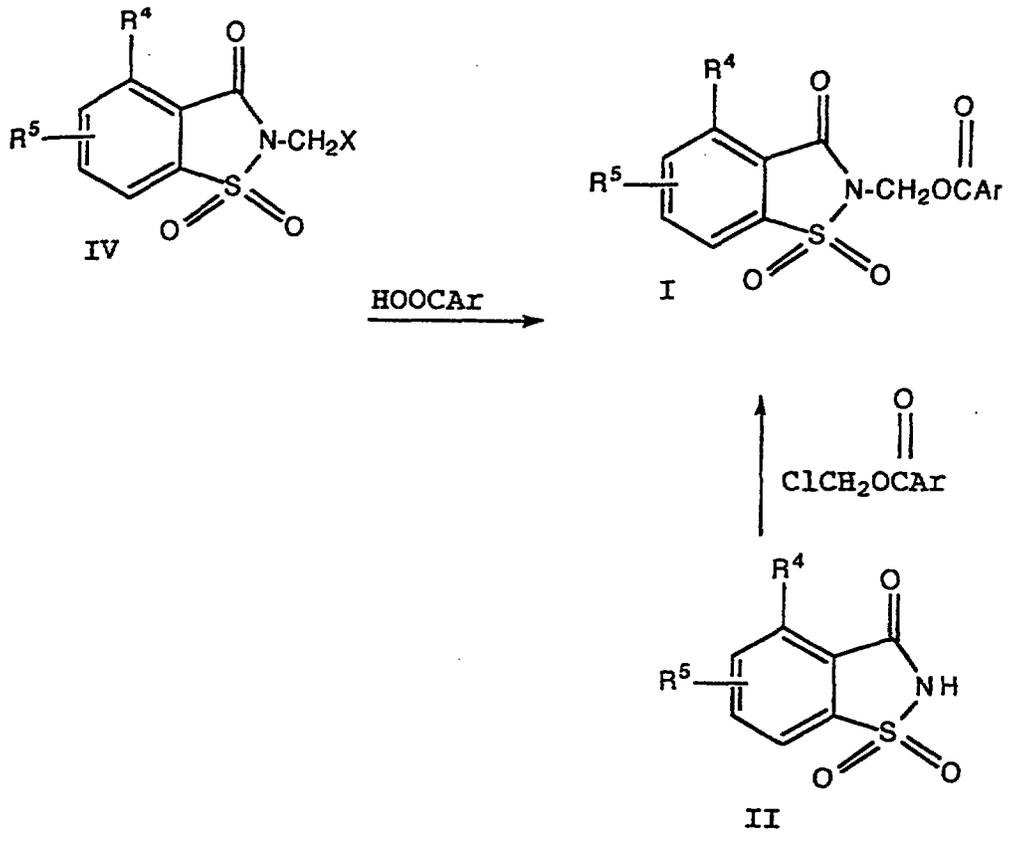
As used herein, the terms hydroxypoly-lower-alkyleneoxy and benzyloxypoly-lower-alkyleneoxy mean such radicals in which poly means 2 to 4, and lower-alkylene in lower-alkyleneoxy means divalent saturated radicals, including branched radicals of from two to about five carbon atoms. The terms thus include $H(OCH_2CH_2)_p-O-$, $H[OCH_2CH(CH_3)]_p-O-$, $C_6H_5CH_2(OCH_2CH_2)_p-O-$, and $C_6H_5CH_2[OCH_2CH(CH_3)]_p-O-$where p=2-4, and the like.

The compounds of the present invention inhibit the activity of serine proteases, specifically human leukocyte elastase and the chymotrypsin-like enzymes, and are thus useful in the treatment of degenerative disease conditions such as emphysema, rheumatoid arthritis, pancreatitis, cystic fibrosis, chronic bronchitis, adult respiratory distress syndrome, inflammatory bowel disease, psoriasis, bullous pemphigoid and alpha-1-antitrypsin deficiency.

The compounds of formula I are prepared by reaction of a 2-halomethylsaccharin with an appropriate aryl carboxylic acid, Ar-COOH or by reaction of a saccharin with a chloromethyl ester of an aryl carboxylic acid as shown in the following reaction scheme where X is a halogen.

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The reaction can either be carried out in the presence of an acid-acceptor, such as an alkali metal carbonate, a trilower-alkylamine or 1,8-diazabicyclo-[5.4.0]undec-7-ene, hereinafter DBU. Alternatively the salt of an alkali metal, especially cesium, or the thallous salt of the aryl carboxylic acid can be used (prepared by reaction of the acid with an alkali metal carbonate or thallous lower-alkoxide); or the salt of an alkali metal, especially the sodium salt, of the aryl carboxylic acid can be used in conjunction with an appropriate trilower-alkylamine as an acid acceptor, preferably diisopropylethylamine. This alkali metal salt can itself be prepared by reaction of the corresponding lower-alkyl ester of the aryl carboxylic acid, preferably the methyl ester, with an aqueous solution of an alkali metal hydroxide, preferably sodium hydroxide, in a lower-alkanol solvent, such as methanol,

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at a temperature in the range of about room temperature up to the boiling point of the solvent used.

The reaction is carried out in an organic solvent inert under the conditions of the reaction, for example acetone, methyl ethyl ketone (MEK), acetonitrile, tetrahydrofuran (THF), diethyl ether, dimethylformamide (DMF), N-methylpyrrolidinone, methylene dichloride (MDC), xylene, toluene or lower-alkanols, at a temperature in the range from ambient up to the boiling point of the solvent used.

The compounds of formula I wherein:

Ar and R^4 are as defined above; R^5 is as defined for group 2) of the compounds and R, N=B, R', X', n, m, A, N=B", R" and N=B"' are as defined above, can also be prepared by the reaction of a 4-R^4-5,-6, or -7-OH-2-saccharinylmethyl aryl carboxylate with

1) an excess of a corresponding alcohol of the R^5 radical [for example, when the R^5 radical is $-O-(CH_2)_n-(5-((CH_2)_n-N=B)-2-furanyl)$ the corresponding alcohol of the R^5 radical is $H-O-(CH_2)_n-(5-((CH_2)_n-N=B)-2-furanyl)$], in the presence of an excess of a tri-loweralkyl- or triarylphosphine, such as tri-n-butyl phosphine or triphenylphosphine, and an excess of a dilower-alkylazodicarboxylate, preferably diethylazodicarboxylate, in a suitable solvent, such as THF, at a temperature of about room temperature or above, preferably at about room temperature; or

2) an excess of a corresponding halide of the R^5 radical [for example, when the R^5 radical is $-O-C(R')_2COOR$ the corresponding halide of the R^5 radical is $X-C(R')_2COOR$, wherein X is halogen], in the presence of an excess of an acid-acceptor, such as potassium carbonate, in a suitable organic solvent, such as DMF or acetone, at a temperature of about room temperature or above, preferably at about room temperature; or

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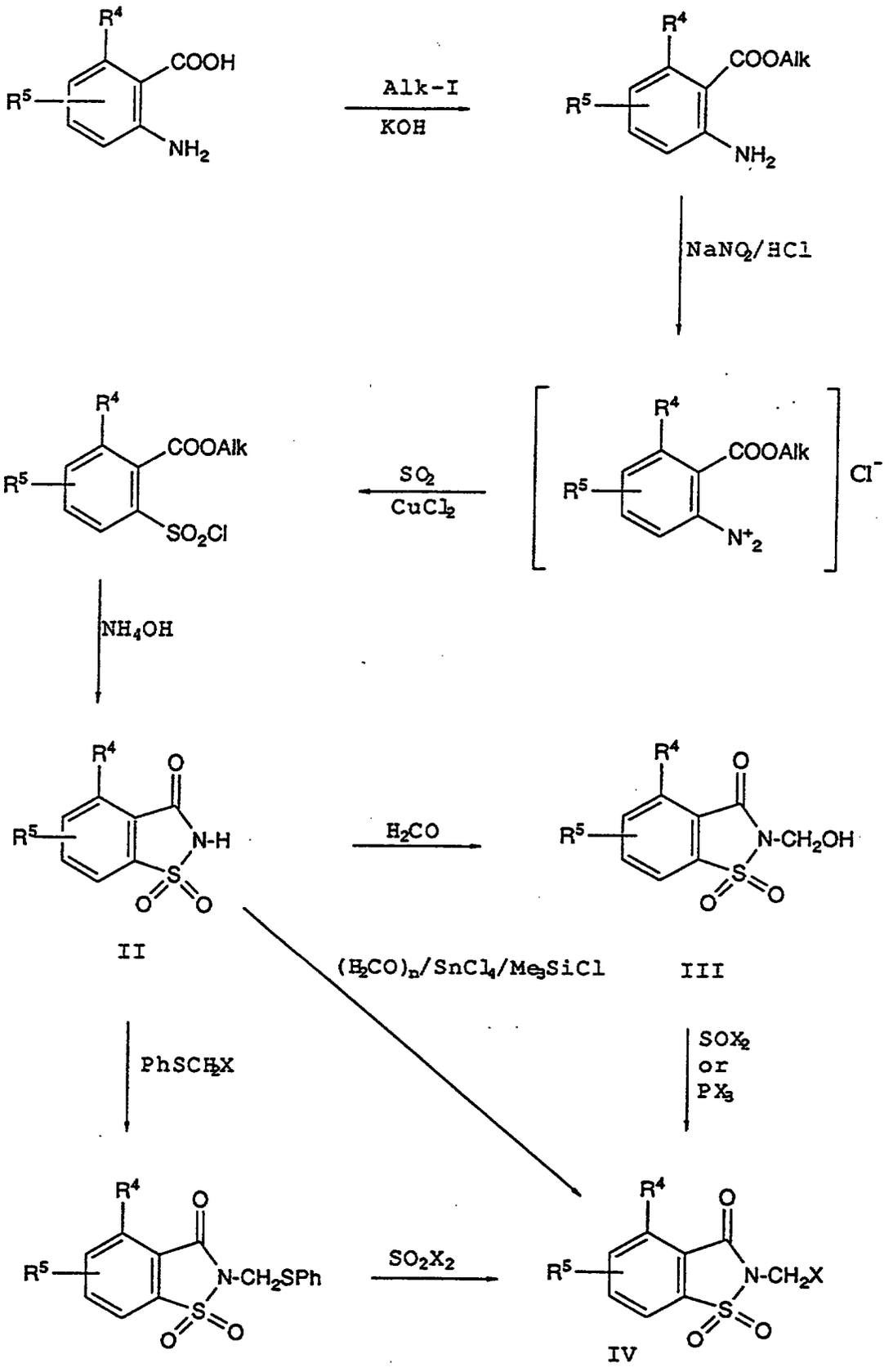


3) at least one mole of an acylating agent of formula XC(O)-N=B", wherein X is halogen, preferably chlorine, and N=B" has the meanings given above, in the presence of at least one mole of an appropriate base, such as DBU, in a suitable organic solvent, e.g. THF, at a temperature of about 0°C or above, preferably at a temperature of about 0°C to about room temperature; or 4) an excess of a sulfamoyl halide such as sulfamoyl chloride or dimethylsulfamoyl chloride, in the presence of an excess of a base, such as DBU, in a suitable solvent, e.g. THF, at a temperature of about 0°C or above, preferably at about 0°C to about room temperature.

The 4-R^4-R^5-2-halomethylsaccharins required for the preparation of the compounds of formula I are prepared by the methods described by D'Alelio et al., J. Macromol. Sci-Chem., A3(5), 941 (1969) and Saari et al., J. Het. Chem., 23, 1253 (1986).

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In the method described by Saari, a methyl ester of an appropriate anthranilic acid is prepared by conventional means from the substituted anthranilic acid and the ester diazotized. The diazonium salt is then reacted with sulfur dioxide and cupric chloride to produce a sulfonyl chloride which is then reacted with concentrated ammonium hydroxide to produce the substituted saccharin derivatives of formula II. The latter, on reaction with formaldehyde in a lower-alkanol solvent, affords the 4-R^4-R^5-2-hydroxymethylsaccharins of formula III, which, on reaction with a thionyl halide or a phosphorus trihalide, afford the corresponding 4-R^4-R^5-2-halomethylsaccharin derivatives of formula IV.

The 4-R^4-R^5-2-halomethylsaccharins of formula IV, where X is chlorine or bromine, can also be prepared by reaction of a corresponding 4-R^4-R^5-2-phenylthiomethylsaccharin with a sulfuryl halide in an inert organic solvent, for example MDC, ethylene dichloride (EDC) or carbon tetrachloride, at a temperature from around 0°C to around 30°C. The 4-R^4-R^5-2-phenylthiomethylsaccharins are in turn prepared by reaction of a 4-R^4-R^5-saccharin of formula II with a halomethylphenyl sulfide in an inert organic solvent, such as toluene, xylene, DMF or MDC at a temperature in the range from ambient up to the boiling point of the solvent used. The reaction can be carried out by reaction of the halomethyl phenyl sulfide with either the thallium salt of the saccharin derivative of formula II (prepared by reaction of the saccharin derivative with a thallium lower-alkoxide in a lower-alkanol); the cesium salt of the saccharin derivative of formula II (prepared by the reaction of the saccharin derivative with cesium carbonate in a lower-alkanol solvent) or with a di-lower-alkyl ammonium salt of the saccharin derivative (prepared as described

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below) in the presence of a tetra-lower-alkyl ammonium halide, such as tetrabutyl ammonium bromide (hereinafter TBAB); or with the saccharin derivative of formula II per se in the presence of a tetralower-alkyl ammonium halide, optionally in the presence also of an alkali metal lower-alkoxide, such as potassium t-butoxide.

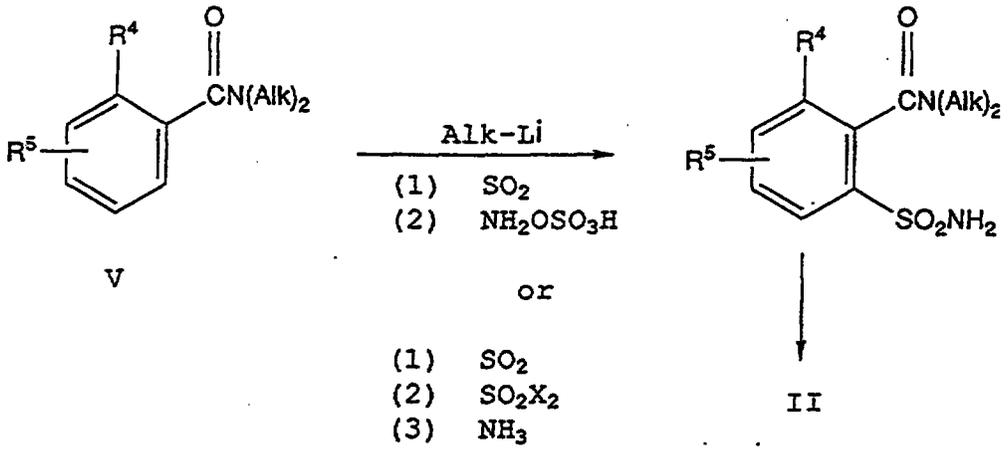
The saccharins of formula II may also be converted to the chloromethyl saccharins of formula IV, wherein X is Cl, in one step by reaction with an excess of formaldehyde or a formaldehyde equivalent, such as paraformaldehyde or 1,3,5-trioxane, and a chlorosilane, preferably chlorotrimethylsilane in the presence of a Lewis acid, preferably a catalytic amount of stannic chloride in an inert solvent, preferably 1,2-dichloro-ethane (ethylene dichloride, EDC).

The compounds of formula II can also be prepared by reaction of a 2-R^4-R^5-N,N-di-lower-alkyl-benzamide of formula V with one molar equivalent of a lower-alkyl alkali metal, such as lithium, optionally in the presence of a tetralower-alkylethylenediamine, in an inert organic solvent, for example THF, and reaction of the resulting alkali metal salt with sulfur dioxide at a temperature in the range from -50°C to -80°C followed either by reaction of the resulting alkali metal sulfinate with hydroxylamine-O-sulfonic acid in the presence of base, or with a sulfuryl halide followed by ammonia. When the sulfur dioxide-hydroxylamine-O-sulfonic acid route is used, it is particularly advantageous to neutralize the hydroxylamine-O-sulfonic acid with one equivalent of sodium hydroxide prior to addition of the alkali metal sulfinate. The resulting 2-R^4-R^5-6-aminosulfonyl-N,N-dilower-alkylbenzamide is thereafter heated in an acid medium to effect cyclization of the latter to produce the dilower-alkyl ammonium salt of the desired 4-R^4-R^5-saccharin of formula II, which can be used as such in the subsequent

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reaction or, if desired, can be hydrolyzed in dilute acid and the free saccharin isolated. It is preferred to carry out the cyclization in refluxing glacial acetic acid. The method is illustrated as follows where R^4, R^5 and Alk have the meanings given above, and the alkali metal is lithium.



The compounds of formula II where R^4 is either primary or secondary lower-alkyl, and which are useful as intermediates for the preparation of the compounds of formula I as described above, are prepared by one of two methods. The compounds of formula II where R^4 is primary lower-alkyl are prepared by reacting a 4-methyl-R^5-saccharin (formula II, R^4 is CH_3) with two molar equivalents of a lower-alkyl lithium in an inert organic solvent, for example THF, and reacting the resulting lithium salt with one molar equivalent of a lower-alkyl halide, both reactions being carried out at a temperature in the range from about -50°C to -80°C.

Another method for preparing the compounds of formula II where R^4 is either primary or secondary lower-alkyl comprises reaction of a 2-primary-lower-alkyl-R^5-N,N-di-lower-alkylbenzamide (formula V, R^4 is primary-lower-alkyl) with one molar equivalent of a lower-alkyl lithium or a lithium dilower-alkylamide,

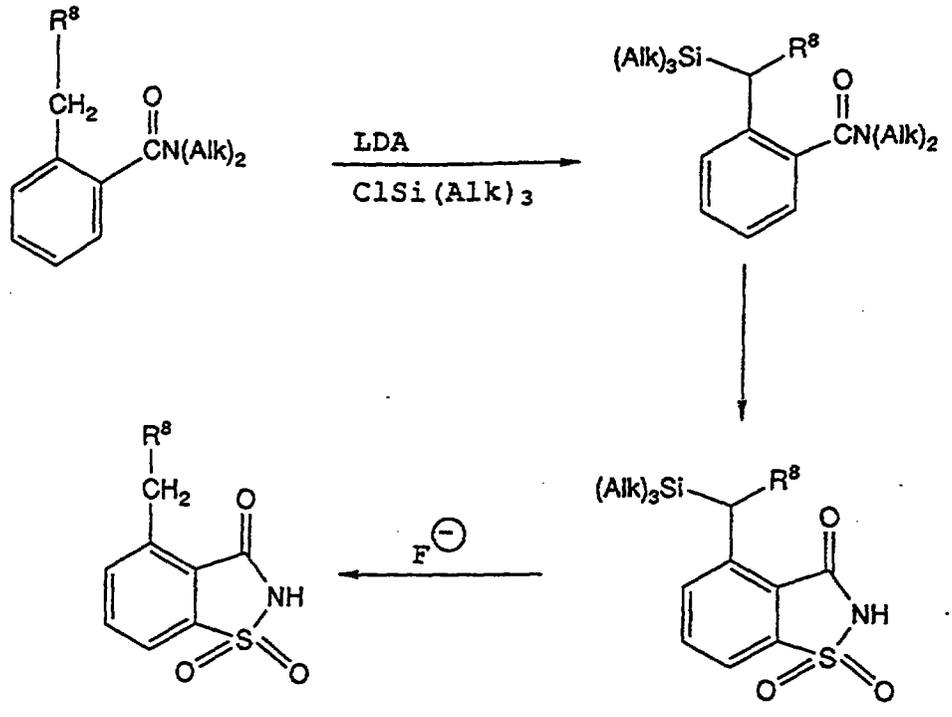
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optionally in the presence of a tetralower-alkyl-ethylenediamine, in an inert organic solvent, for example THF, and reaction of the resulting lithium salt with one molar equivalent of a lower-alkyl halide at a temperature in the range from about -50°C to -80°C. The resulting 2-primary or secondary-lower-alkyl-R^5-N,N-di-lower-alkylbenzamide is thereafter converted to the compounds of formula II, where R^4 is primary or secondary lower-alkyl, by the same sequence of reactions described above When the 2-lower-alkyl group in the 2-lower-alkyl-R^5-N,N-di-lower-alkyl-benzamide starting material is methyl, alkylation affords species where the 2-lower-alkyl group is either straight or branched depending upon whether a straight or branched chain lower-alkylhalide is used for the alkylation. On the other hand, when the 2-lower-alkyl group in the starting material contains more than one carbon atom, alkylation takes place on the carbon atom adjacent the benzene ring and affords products having a sec.-lower-alkyl group at the 2-position.

A particularly useful method for the preparation of compounds II where R^4 is n-lower-alkyl and R^5 is hydrogen involves the protection of the benzylic protons of the starting material V with a trialkylsilyl group, thereby permitting lithiation at the 6-position and formation of the sulfonamide as described above.

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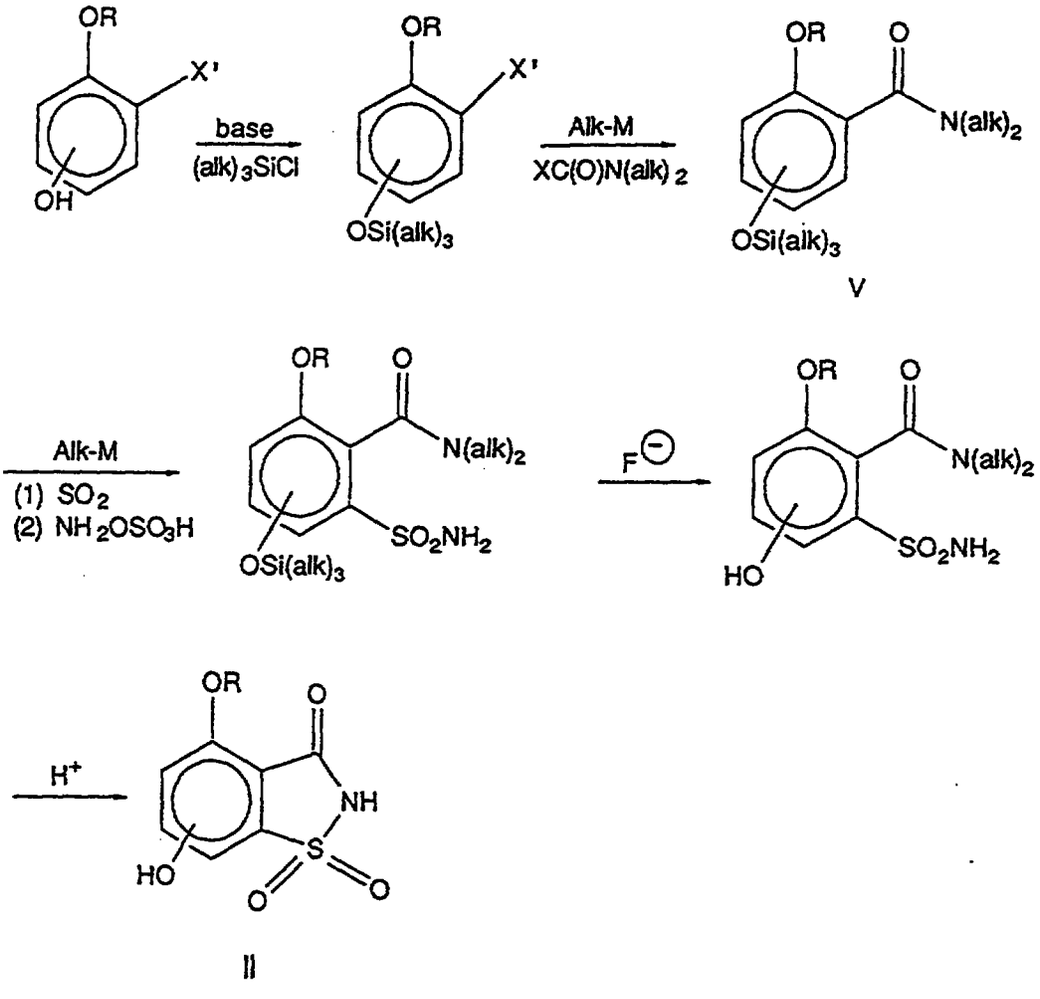




A 2-n-lower-alkylbenzamide wherein R^8 is lower-alkyl is silylated by forming the benzylic anion using an alkyllithium or, preferably, a lithium dialkylamide in an inert solvent, preferably THF, and treating with a suitable chlorotrialkylsilane, preferably chlorotrimethylsilane. The saccharin is synthesized as before, and the silyl group is removed by treatment with a source of fluoride anion, preferably cesium fluoride in DMF or tetra-n-butylammonium fluoride in an inert solvent.

A preferred method for preparing compounds of the Formula II wherein R^4 is lower-alkoxy and R^5 is hydroxy involves

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II

the treatment of a 1-halo-2-lower-alkoxy-R^5-hydroxy-benzene, wherein X' is a halogen, preferably bromine, with an excess of a chlorotrialkylsilane in the presence of an excess of a base, preferably imidazole, in a suitable solvent, e.g. DMF, at a temperature of room temperature or above, preferably at about room temperature, to produce a 1-halo-2-lower-alkoxy-R^5-tri-lower-alkylsilyloxybenzene. Treatment of the latter compound with a molar equivalent of a di-lower-alkyl-carbamoyl halide, preferably a di-lower-alkylcarbamoyl-chloride, in the presence of an excess of a lower-alkyl alkali metal (Alk-M, wherein Alk is a lower-alkyl group and M is an alkali metal), e.g. n-BuLi, in a suitable

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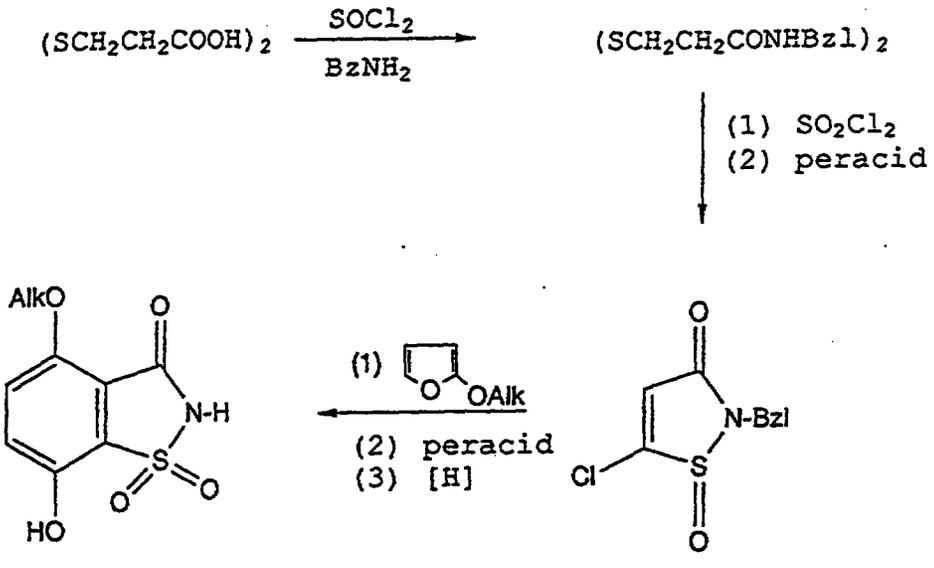
solvent, such as ether, at a temperature of about 0°C or below, preferably 0°C to -78°C, to produce the corresponding 2-lower-alkoxy-R^5-tri-lower-alkylsilyloxy-N,N-dilower-alkylbenzamide (Formula V, R^4 is lower-alkoxy, and R^5 is trilower-alkylsilyloxy). Treatment of the latter compound with an excess of a lower-alkyl alkali metal (Alk-M), preferably sec-BuLi, in the presence of at least one molar equivalent of a tetra-lower-alkylethylenediamine, e.g. N,N,N'N'-tetramethyl-ethylenediamine in an inert organic solvent, e.g. THF, at a temperature below about 0°C, preferably at -78°C, followed by reaction of the resulting alkali metal salt with sulfur dioxide at a temperature below about 15°C, preferably at -78°C; followed by reaction of the resulting alkali metal sulfinate in water with an excess of hydroxylamine-O-sulfonic acid, which has been neutralized with one equivalent of sodium hydroxide prior to its addition to the alkali metal sulfinate, at a temperature below about room temperature, preferably at a temperature in the range of about 0°C up to about room temperature, affords a 2-aminosulfonyl-6-lower-alkoxy-R^5-tri-lower-alkyl-silyloxy-N,N-dilower-alkyl-benzamide. The silyl group is then removed by treatment with a) a source of a fluoride anion, preferably an excess of tetra-n-butylammonium fluoride in an inert solvent, e.g. THF, at a temperature below about room temperature, preferably at a temperature in the range of about 0°C up to about room temperature; or
b) with an excess of potassium fluoride in a suitable solvent, e.g. DMF, in the presence of a catalytic amount of an acid, preferably 48% HBr, at a temperature of about room temperature to produce a 2-aminosulfonyl-6-lower-alkoxy-R^5-hydroxy-N,N-di-lower-alkylbenzamide. Refluxing the latter compound with an acid, preferably glacial acetic acid, then produced the corresponding 4-lower-alkoxy-R^5-hydroxysaccharin derivative of

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formula II, as the dilower-alkylammonium salt.

Access to certain of the required intermediates in some cases requires building up the two rings making up the saccharin nucleus. Thus to prepare saccharins where R^4 is lower-alkoxy and R^5 is 7-hydroxy, the following synthesis may be used:

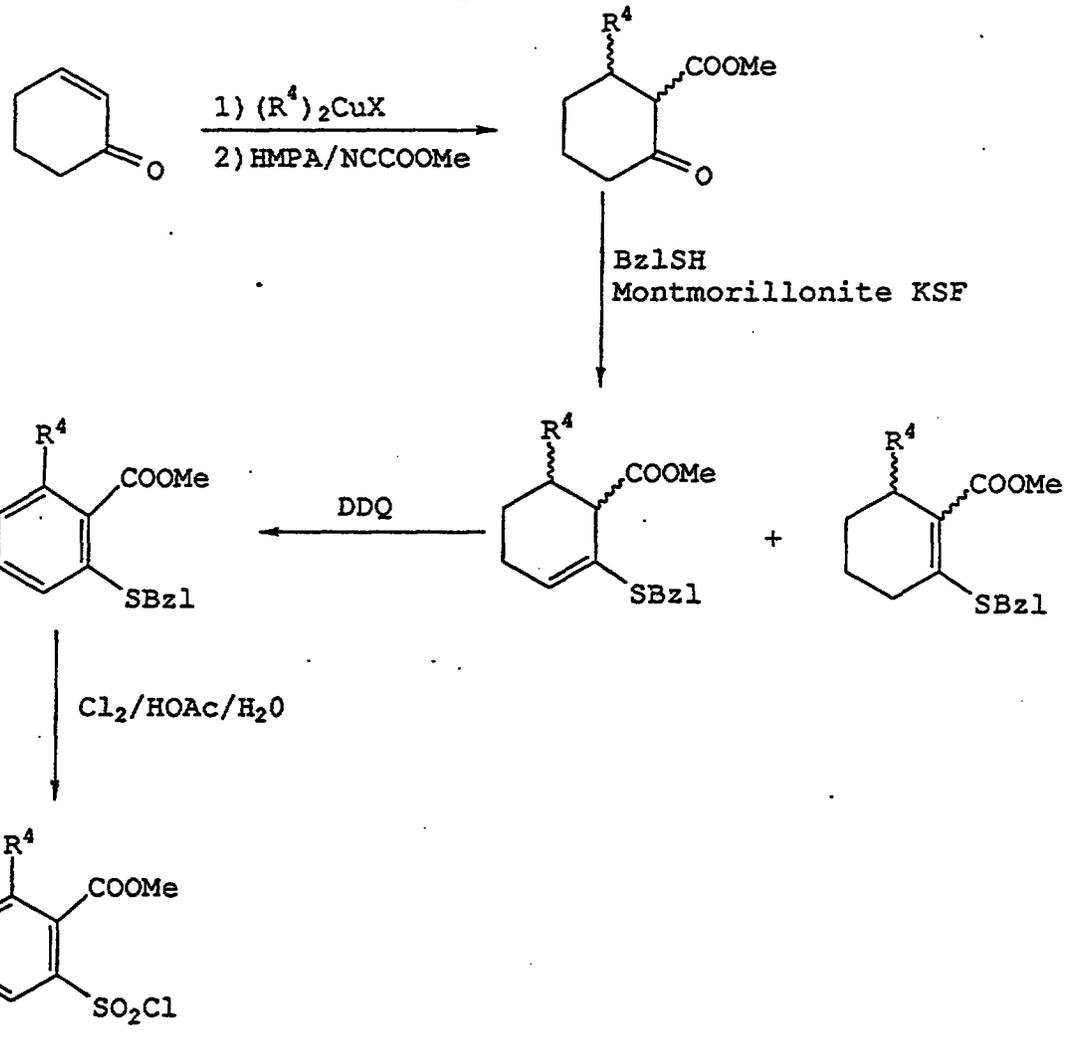


3,3-Dithiobispropionic acid is converted to the bis acid chloride by reaction of the acid with thionyl chloride, and the acid chloride is then reacted with four molar equivalents of benzylamine to produce the bis N-benzylamide. The latter, on reaction with sulfuryl chloride in an organic solvent, such as MDC, EDC or carbon tetrachloride, affords 5-chloro-2-benzyl-2H-isothiazol-3-one, which is oxidized with one molar equivalent of a peracid, such as perbenzoic acid or 3-chloroperbenzoic acid, to 5-chloro-2-benzyl-2H-isothiazol-3-one-1-oxide. The latter, on heating under pressure with a 2-lower-alkoxyfuran in an organic solvent, such as benzene, toluene or xylene, affords a 4-lower-alkoxy-7-hydroxy-2-benzyl-1,2-benzisothiazol-2H-3-one-1-oxide. The 7-hydroxy group can, if desired, then be reacted with a lower-alkyl halide or a lower-

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alkoxypoly-lower-alkoxy-lower-alkyl halide to give the corresponding 4,7-di-lower-alkoxy or 4-lower-alkoxy-7-lower-alkoxypoly-lower-alkoxy-2-benzyl-1,2-benziso-thiazol-2H-3-one-1-oxide. Further oxidation of the product with one molar equivalent of a peracid as described above followed by catalytic debenzylation by transfer hydrogenation affords the corresponding 4-lower-alkoxy-7-hydroxysaccharins.

Compounds of formula II wherein R^4 is lower-alkyl or phenyl and R^5 is hydrogen may be synthesized by an alternate route from 2-cyclohexenone:



2-Cyclohexenone is reacted with the appropriate cuprate followed by methyl cyanoformate

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according to the method of Winkler et al. [Tet. Lett. 1987, 1051 and J. Org. Chem. 54, 4491 (1989)]. The resulting β-ketoester is reacted with benzylmercaptan in the presence of the acidic clay Montmorillonite KSF to produce a mixture of regioisomers of the benzylthioenol ether. The mixture is aromatized by treatment with dichlorodicyanobenzoquinone (DDQ) and oxidized with chlorine gas in aqueous acid to provide the sulfonyl chloride ester, which may then be converted to the intermediate II as shown earlier.

The aryl carboxylic acids, Ar-COOH, used to prepare the final products of formula I are members of a known class and can be prepared by well-known, conventional synthetic methods.

Chloromethyl esters of the aryl carboxylic acid may be prepared by treating the carboxylic acid with formaldehyde or a formaldehyde equivalent, preferably paraformaldehyde, in the presence of (1) a chloro acid, preferably zinc chloride or hydrochloric acid, or (2) trimethylsilyl chloride plus stannic chloride.

Simple chemical transformations which are conventional and well known to those skilled in the art of chemistry can be used for effecting changes in functional groups in the compounds of the invention. For example, catalytic reduction of nitro groups to produce the corresponding amino substituted compounds, acylation of amino-substituted species to prepare the corresponding amides, oxidation of sulfides or sulfoxides to prepare the corresponding, respective sulfoxides or sulfones, saponification of esters to produce the corresponding carboxylic acids, catalytic debenzylation of phenolic ethers or of benzylamines to produce the corresponding phenols or debenzylated amines, alkylation of phenols or alcohols with alkylating agents in the presence of base to produce

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ethers, reaction of phenols or alcohols with other alcohols in the presence of dehydrating reagents (e.g. triphenylphosphine/diethylazodicarboxylate, or tri-n-butylphosphine/diethylazodicarboxylate) to produce the corresponding ethers, catalytic removal of N-carbobenzyloxy protecting groups in the presence of formaldehyde to produce the corresponding N-methyl derivatives, catalytic debenzylation of benzyl ethers to produce the corresponding alcohols, catalytic debenzylation of benzyl esters to produce the corresponding carboxylic acids, reaction of alcohols with acids in the presence of dehydrating reagents (e.g. dicyclohexylcarbodiimide/dimethylaminopyridine) to produce the corresponding esters, the hydrolysis of t-butylesters in the presence of trifluoroacetic acid to produce the corresponding acids, conversion of acids into the corresponding acid halides, or acylation of acid halides with amines to afford the corresponding amides, as desired can be carried out. It will also be appreciated that these simple chemical transformations are equally applicable for effecting changes in functional groups of the intermediates which are useful in the preparation of the final products of the invention.

In standard biological test procedures, the compounds of formula I have been found to possess human leukocyte elastase (HLE) and chymotrypsin inhibitory activities, and are thus useful in the treatment of degenerative diseases, such as emphysema, rheumatoid arthritis, pancreatitis, cystic fibrosis, chronic bronchitis, adult respiratory distress syndrome, inflammatory bowel disease, psoriasis, bullous pemphigoid and alpha-1-antitrypsin deficiency.

The compounds of formula I having basic functions can be converted to the acid-addition salt form by interaction of the base with an acid. In like

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manner, the free base can be regenerated from the acid-addition salt form in conventional manner, that is by treating the salts with cold, weak aqueous bases, for example alkali metal carbonates and alkali metal bicarbonates. The bases thus regenerated can be interacted with the same or a different acid to give back the same or a different acid-addition salt. Thus the bases and all of their acid-addition salts are readily interconvertible.

Likewise certain compounds of formula I having acid, i.e. carboxylic acid, functions can be converted to salt forms thereof by reaction of the acid with a base, such as alkali metal or ammonium hydroxide or with organic bases such as alkyl, dialkyl or tri-alkylamines, and the acids can be regenerated from the salts by treatment of the salts with aqueous acids.

It will thus be appreciated that formula I not only represents the structural configuration of the bases and acids, but is also representative of the structural entities which are common to all of the compounds of formula I whether in the form of the free base, the free acids or in the form of the salts of the bases and acids. It has been found that, by virtue of these common structural entities, the compounds of formula I and their salts have inherent pharmacological activity of a type to be more fully described hereinbelow. This inherent pharmacological activity can be enjoyed in useful form for pharmaceutical purposes by employing the free bases or free acids themselves or the salts formed from pharmaceutically acceptable acids and bases; that is, acids or bases whose anions or cations are innocuous to the animal organism in effective doses of the salts so that beneficial properties inherent in the common structural entity represented by the free bases and free acids are not vitiated by side effects ascribable to the anions or cations.

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In utilizing this pharmacological activity of the salt, it is preferred, of course, to use pharmaceutically acceptable salts. Although water insolubility, high toxicity or lack of crystalline character may make some particular salt species unsuitable or less desirable for use as such in a given pharmaceutical application, the water-insoluble or toxic salts can be converted to the corresponding pharmaceutically acceptable bases by decomposition of the salts with aqueous base or aqueous acid as explained above, or alternatively they can be converted to any desired pharmaceutically acceptable salt by double decomposition reactions involving the anion or cation, for example by ion-exchange procedures.

Moreover, apart from their usefulness in pharmaceutical applications, the salts are useful as characterizing or identifying derivatives of the free bases or free acids or in isolation or purification procedures. Like all of the salts, such characterization or purification salt derivatives can, if desired, be used to regenerate the pharmaceutically acceptable free bases or free acids by reaction of the salts with aqueous base or aqueous acid, or alternatively they can be converted to a pharmaceutically acceptable salt by, for example, ion-exchange procedures.

The novel feature of the compounds then resides in the concept of the 2-saccharinylmethyl aryl carboxylates of formula I and not in any particular acid or base moiety or acid anion or base cation associated with the salt forms of the compounds.

The compounds of formula I of the invention can be prepared for pharmaceutical use by incorporating them in unit dosage form as tablets or capsules for oral administration either alone or in combination with suitable adjuvants such as calcium carbonate, starch,

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lactose, talc, magnesium stearate, gum acacia and the like. Still further, the compounds can be formulated for oral, parenteral or aerosol inhalation administration either in aqueous solutions of water soluble salts of the compounds or in aqueous alcohol, glycol or oil solutions or oil-water emulsions in the same manner as conventional medicinal substances are prepared.

The percentages of active component in such compositions may be varied so that a suitable dosage is obtained. The dosage administered to a particular patient is variable, depending upon the clinician's judgment using as criteria: the route of administration, the duration of treatment, the size and physical condition of the patient, the potency of the active component and the patient's response thereto. An effective dosage amount of the active component can thus only be determined by the clinician after a consideration of all criteria and using his best judgment on the patient's behalf.

The molecular structures of the compounds of the invention were assigned on the basis of study of their infrared and NMR spectra. The structures were confirmed by the correspondence between calculated and found values for elementary analyses for the elements or by analysis of the high-resolution mass spectra.

The invention will now be illustrated with reference to the following examples but is in no way to be construed as limited thereto. All melting points are uncorrected.

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Preparation of Starting Materials

1. Preparation of 2-chloromethyl-4-methylsaccharin [IV; R^4=Me; R^5=H; X=Cl]

Powdered potassium hydroxide (7.4 g, 0.132 mol) was admixed with dimethyl sulfoxide (DMSO) (100 ml), and the mixture was stirred for 5 minutes. 6-Methylanthranilic acid (10.0 g, 0.066 mol) was then added to the mixture and iodomethane (4.52 ml, 0.073 mol) added dropwise. The reaction mixture was stirred for 30 minutes at room temperature, then diluted with 250 ml ether, washed with water (3 x 100 ml), dried over magnesium sulfate and concentrated. The crude product was filtered through a pad of flash grade (32-63) silica gel and eluted with 1:9 ether:hexane to afford 4.23 g (39%) of methyl 6-methylanthranilate as an oil.

The methyl 6-methylanthranilate so prepared (4.23 g, 0.026 mol) was dissolved in 25 ml acetic acid and the solution cooled to 0°C. Concentrated hydrochloric acid (45 ml) was added to produce a tan slurry. A solution of 1.89 g (0.027 mol) sodium nitrite in 8 ml water was added dropwise with stirring, the resulting orange solution was stirred at 0°C for 1 hour and then added in 6 portions to a mixture of 2.18 g (0.013 mol) cupric chloride dihydrate and sulfur dioxide (6.3 g) in 33 ml acetic acid and 6 ml water at 0°C. The dark green solution was stirred at room temperature overnight, poured into 300 ml ice-water, and the solid which separated was collected and dried by suction to provide 1.11 g of methyl 2-chlorosulfonyl-6-methyl-benzoate which was immediately added to 100 ml ice cold ammonium hydroxide and stirred at room temperature overnight. The solution was acidified to pH 1 with concentrated hydrochloric acid, and the resulting precipitate was collected and air-dried to provide 729 mg (12%) of 4-methylsaccharin [II], mp 224-226°C.

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A mixture of 1.0 g (0.005 mol) 4-methylsaccharin, 0.33 g (0.001 mol) TBAB and 1.2 g 0.0075 mol) of chloromethyl phenyl sulfide in 25 ml toluene was heated under reflux for about sixteen hours and then cooled, diluted with ethyl acetate and the solution washed with aqueous bicarbonate and water. The organic layer was dried and taken to dryness to give 0.74 g of 2-phenylthiomethyl-4-methylsaccharin..

The latter (0.74 g, 0.002 mol) was dissolved in 25 ml MDC and the solution treated dropwise over a period of about two hours with stirring with a solution of 0.47 g (0.003 mol) sulfuryl chloride in MDC and the reaction mixture taken to dryness. The yellow residual solid was triturated with hexane and filtered and dried to give 0.46 g of the desired product as a pale yellow solid.

2. Preparation of 2-chloromethyl-4-chlorosaccharin [IV; R^4=Cl; R^5=H; X=Cl]

Using the procedure described above in Preparation 1, 5.0 g (0.029 mol) 6-chloroanthranilic acid and 2.75 ml (0.044 mol) iodomethane were reacted in the presence of 4.08 g (0.073 mol) powdered potassium hydroxide to give 4.22 g (78%) of methyl 6-chloroanthranilate as an oil.

4-Chlorosaccharin was prepared by the same method as used for the preparation of 4-methylsaccharin using 4.22 g (0.023 mol) methyl 6-chloroanthranilate in 22 ml acetic acid and 40 ml concentrated hydrochloric acid and 1.68 g (0.024 mol) sodium nitrite in 7 ml water to prepare the diazonium salt which was added to 1.93 g (0.011 mol) cupric chloride dihydrate and 6.5 g sulfur dioxide in 30 ml acetic acid and 5 ml water. The resulting methyl 2-chlorosulfonyl-6-chlorobenzoate was treated with 150 ml ammonium hydroxide as described above to afford 3.07 g (62%) of 4-chlorosaccharin [II] as a pale yellow solid, mp 245-246°C.

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2-Hydroxymethyl-4-chlorosaccharin [III] was prepared by heating a solution of 1.00 g (0.0046 mol) of 4-chlorosaccharin and 3.22 ml aqueous 37% formalin in ethanol. All attempts to crystallize the viscous oily product resulted in decomposition to the starting material, and the product was thus used in the next step without characterization.

The crude 2-hydroxymethyl-4-chlorosaccharin so prepared (609 mg, 0.0025 mol) was admixed with 5 ml diethyl ether, and 3 ml thionyl chloride was added. The resulting mixture was heated to effect complete solution, stirred at room temperature overnight, diluted with 20 ml ether and filtered through a pad of celite topped with sand and eluted with ether. Removal of the solvent afforded 430 mg crude chloromethyl derivative. A portion (225 mg) was removed for further reactions. The remainder (205 mg) was flash chromatographed on silica gel and eluted with 40% ether/pentane to provide 137 mg of the desired product, mp 135-136°C.

3A. Preparation of 2-chloromethyl-4-phenylsaccharin [R_4=Ph; R^5=H; X=Cl]

To a suspension of 6.0 g (0.03 mol) cuprous iodide in 100 ml THF was added 25 ml dimethyl sulfide, and the resulting yellow solution was cooled to -78°C and treated dropwise with a solution of 23 ml (0.06 mol) of a 3.0 M solution of phenyl magnesium bromide in diethyl ether. The resulting pale yellow-orange solution was stirred at -78°C under nitrogen for one hour and then treated with 3.02 g (0.03mol) of 2-cyclohexenone in 10 ml THF. The resulting mixture was allowed to warm to 0°C over a two hour period, recooled to -78°C, treated with 15 ml hexamethylphosphoramide, stirred for thirty minutes, treated with 8.0 g (0.09 mol) of methyl cyanoformate and allowed to warm to ambient temperature overnight. The reaction mixture was poured into 100 ml 2N hydrochloric acid, and the organic

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phase was separated and the aqueous phase back-extracted with MDC. The combined organic extracts were taken to dryness in vacuo and the residue triturated with saturated ammonium chloride, then with water, then with brine and taken to dryness once again to give 3.2 g of methyl 2-phenylcyclohexan-6-one carboxylate as an oil.

The latter (3.0 g, 0.013 mol), 4.8 g (0.039 mol) benzyl mercaptan and 1.0 g of Amberlyst®-15 resin (Rohm and Haas) in chloroform was heated under reflux for twenty hours, the mixture treated with an additional 1.5 g of the resin and heated for an additional four hours. The mixture was then cooled to ambient temperature, filtered, the filtrate taken to dryness in vacuo, the residue triturated with hexane and the solid collected by filtration to give 0.85 g (19%) of a mixture of methyl 2-benzylthio-6-phenylcyclohex-2-ene carboxylate and methyl 2-benzylthio-6-phenyl-cyclohex-1-ene carboxylate, 0.6 g (0.0018 mol) of which was heated with 2.0 g 2,3-dichloro-5,6-dicyanobenzo-quinone in 25 ml toluene with stirring under nitrogen for twenty-four hours. The mixture was filtered through a pad of silica gel, eluting with 2:1 MDC:hexane, and the eluate was taken to dryness to give 0.3 g (67%) of methyl 2-benzylthio-6-phenylbenzoate.

The latter (0.52 g, 0.0016 mol) dissolved in 10 ml MDC was diluted with 20 ml acetic acid and 5 ml water, the mixture cooled to -10°C, and chlorine gas was bubbled through the mixture until the exothermic reaction subsided. The mixture was then stirred for ten minutes and taken to dryness in vacuo to give 0.41 g (85%) of methyl 2-chlorosulfonyl-6-phenylbenzoate which was dissolved in 10 ml THF and added to 25 ml solution of concentrated ammonium hydroxide while cooling in an ice/acetone bath. The reaction mixture was extracted with MDC, the organic phase discarded, and the aqueous layer acidified to pH 1 with concentrated hydrochloric

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acid and extracted with MDC. The organic extracts, on washing with brine, drying and evaporation to dryness, afforded 0.33 g (97%) 4-phenylsaccharin [II].

Following a procedure similar to that described in Preparation 1, the latter (0.33 g, 0.0012 mol) was reacted with 0.3 g (0.0019 mol) chloromethyl phenyl sulfide in 15 ml toluene in the presence of 0.08 g (0.0025 mol) of TBAB and the product, 2-phenylthiomethyl-4-phenylsaccharin (0.48 g, 100%), treated with sulfuryl chloride in MDC to give 0.36 g (95%) of the desired product.

3B. Preparation of 2-chloromethyl-4-(1,1-dimethylethyl)saccharin. [IV; R_4=1,1-diMeEt; R^5=H; X=Cl]

To a suspension of anhydrous CuCN (2.16 g, 0.025 mol) in anhydrous ether (100 ml) at -78°C was added t- butyllithium (29.0 ml 1.7 M solution in pentane, 0.05 mol). After being stirred at -78°C for 1 hr and at -45°C for 30 minutes, the reaction mixture was recooled to -78°C. A solution of cyclohexenone (2.4 g,0.025 mol) in ether (25 ml) was added and stirring continued for 15 minutes at -78°C and at -45°C for 30 minutes. The resulting mixture was recooled to -78°C, and HMPA (10 ml) in ether (25 ml) was added. After 5 min, methyl cyanoformate (2.55 g, 0.03 mol) in ether (25 ml) was added and the reaction warmed to 0°C over a 2 hr period. The resulting mixture was quenched with 2N HCl (100 ml), the layers were separated, and the organic phase was washed with saturated NH_4Cl solution (3 x 50 ml), water (2 x 50 ml), brine (1 x 50 ml) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification by Kugelrohr distillation (bath temperature 100-115°C at 0.6 mm) afforded 4.7 g (88%) of methyl 2-(1,1-dimethylethyl)cyclohexan-6-one-carboxylate.

The cyclohexanone (4.6 g, 0.022 mol) was mixed with benzylmercaptan (2.95 g, 0.024 mol) and the acidic clay montmorillonite, KSF (7.5 g) in anhydrous

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toluene (7.5 ml). The mixture was refluxed under nitrogen with azeotropic removal of water for 6 hr, cooled to room temperature and let stand overnight. The solids were filtered off and washed with ether. The combined filtrate was washed with 10% Na_2CO_3, water, brine and dried. Removal of the solvent in vacuo and purification of the residue by flash chromatography on silica gel (10% ether in hexanes) gave 4.4 g (66% of a mixture of methyl 2-benzylthio-6-(1,1-dimethylethyl)-cyclohex-2-ene carboxylate and methyl 2-benzylthio-6-(1,1-dimethylethyl)cyclohex-1-ene carboxylate, which was stirred with DDQ (17.5 g, 0.077 mol) in toluene (50 ml) for 16 hr. The red reaction mixture was filtered through a 15 cm pad of silica gel, eluting with 6:3:1 hexanes:MDC:ether (1000 ml). The eluents were washed with 10% NaOH solution, water, brine and dried. Removal of the solvent in vacuo and purification by chromatography on silica gel (5% ether in hexanes) gave 1.6 g (40%) of methyl 2-benzylthio-6-(1,1-dimethyl)-benzoate.

The benzylthiobenzoate (1.3g, 0.004 mol) dissolved in MDC (5 ml) was diluted with acetic acid (25 ml) and water (2 ml), the mixture cooled to -10°C, and chlorine gas was bubbled until the exothermic reaction subsided. the mixture was then stirred for 10 minutes and taken to dryness in vacuo. Purification of the residue by flash chromatography on silica gel (1:1 hexanes:MDC) gave 0.8 g (67%) of methyl 2-chloro-sulfonyl-6-(1,1-dimethylethyl)benzoate, which was dissolved in THF (5 ml) and added to a solution of concentrated ammonium hydroxide (25 ml) while cooling in an ice/acetone bath. After stirring at room temperature for 16 hr, the reaction mixture was concentrated in vacuo and acidified to pH 1 with 2N HCl. The separated solids were collected by filtration and crystallized from ether to give 0.64 g (95%) of

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4-(1,1-dimethylethyl)saccharin [II], mp 185-187°C.

The 4-(1,1-dimethylethyl)saccharin (0.025 g 1.0 mmol) was mixed with chloromethyl phenyl sulfide (0.25 g, 1.5 mmol) and TBAB (0.2 g, 0.6 mmol) in toluene (25 ml) and refluxed under nitrogen for 16 hr. The resulting mixture was cooled to room temperature, evaporated to dryness and purified by chromatography on silica gel (80%) MDC in hexanes) to give 0.35 g (98%) of 2-phenylthiomethyl-4-(1,1-dimethylethyl)saccharin, which was treated with sulfuryl chloride (0.25 g, 1.8 mmol) in MDC to give 0.21g (75%) of the desired product.

4. Preparation of 2-chloromethyl-4-bromosaccharin [IV; R^4=Br; R^5=H; X=Cl]

A mixture of 3.22 g (0.012 mol) 4-bromosaccharin [Japanese Pat. Pubn. 58/79,034; C.A. 100, 7773w (1984)], 1.63 g (0.015 mol) potassium t-butoxide, 0.39 g (0.0012 mol) TBAB and 3.0 ml (0.022 mol) chloromethyl phenyl sulfide in 100 ml toluene was heated under reflux under a nitrogen atmosphere for eight hours and then stirred at ambient temperature for about sixteen hours. The reaction mixture was then diluted with ethyl acetate, and the organic layer was washed with dilute potassium carbonate, water and brine, dried over magnesium sulfate and taken to dryness in vacuo. The residual solid was recrystallized from toluene-hexane to give 3.86 g (84%) of 4-bromo-2-phenylthiomethyl-saccharin, mp 174.5-178°C.

To a solution of the latter (3.27 g, 0.0085 mol) in 85 ml MDC was added, dropwise with stirring, 1.02 ml (0.0127 mol) sulfuryl chloride. The mixture was stirred at ambient temperature for an hour and a half, concentrated in vacuo and the residue triturated with hexane and filtered to give 2.61 g crude product which was recrystallized from toluene-hexane to give 2.24 g (85%) of the desired product, mp 157-159°C.

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5. Preparation of 2-chloromethyl-4-methoxysaccharin [IV; R^4=MeO; R^5=H; X=Cl]

To a solution of 8.0 ml (0.053 mol) tetramethylethylenediamine (TMEDA) in 350 ml THF at -70°C was added 42 ml (0.055 mol) of a 1.3 M solution of s-butyl lithium in cyclohexane and the mixture was stirred for fifteen minutes. To the solution was added dropwise with stirring a solution of 10.36 g (0.050 mol) of 2-methoxy-N,N-diethylbenzamide [V] in 150 ml THF while maintaining the temperature at -60°C or below. After stirring for 20 minutes sulfur dioxide was bubbled into the reaction mixture, keeping the reaction temperature below -50°C, until the reaction mixture was acid to wet litmus paper. The mixture was stirred at ambient temperature for two hours, diluted with 450 ml hexane, and the solid material which had separated was collected, dissolved in 200 ml water and the mixture treated with 65 g sodium acetate and 21.5 g (0.19 mol) of hydroxylamine-O-sulfonic acid in portions with stirring. The white solid which separated was collected and dried to give 7.04 g (49%) of 2-aminosulfonyl-6-methoxy-N,N-diethylbenzamide, mp 190-194.5°C.

A mixture of the product (4.3 g, 0.015 mol) in 75 ml dioxane and 25 ml concentrated hydrochloric acid was heated on a steam bath for 70 hours, then cooled, concentrated in vacuo, diluted with water and ice and rendered strongly basic with concentrated sodium hydroxide. The mixture was washed with MDC, and the aqueous layer was acidified with dilute hydrochloric acid and extracted with MDC. The extracts were dried over magnesium sulfate and taken to dryness to give 1.29 g (40%) of 4-methoxysaccharin [II]. In an alternative, and preferred, procedure, cyclization of 2-aminosulfonyl-6-methoxy-N,N-diethylbenzamide to 4-methoxysaccharin in 65% yield was carried out in refluxing glacial acetic acid for six and a half hours.

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Following a procedure similar to that described in Preparation 4 above, 1.14 g (0.0053 mol) of the latter was reacted with 1.31 ml (0.0097 mol) chloromethyl phenylsulfide in toluene in the presence of 0.72 g (0.0064 mol) potassium t-butoxide and 174 mg (0.00054 mol) TBAB to give 1.23 g (69%) of 4-methoxy-2-phenylthiomethylsaccharin, mp 152.5-154.5°C (from ethyl acetate-hexane), 1.02 g (0.003 mol) of which was treated with 0.36 ml (0.0045 mol) sulfuryl chloride in MDC to give 282 mg (36%) of the desired product, mp 169-174°C.

6A. Preparation of 2-chloromethyl-4-sec-butylsaccharin [IV; R^4=sec.-Bu; R^5=H; X=Cl]

To a solution of 4.74 ml (0.031 mol) TMEDA in 300 ml THF (passed through alumina prior to use) was added 5.8 g (0.03 mol) 2-ethyl-N,N-diethylbenzamide [V]. The solution was cooled to -78°C and treated with 34.9 ml (0.031 mol) of a 0.9 M solution of s-butyl lithium in cyclohexane. When addition was complete, the mixture was stirred for twenty minutes and then treated with a solution of 3.2 ml (0.04 mol) ethyl iodide while maintaining the temperature at -78°C. The temperature was then allowed to rise to ambient temperature and the mixture stirred for about sixteen hours and then poured into water. The resulting oil was separated and chromatographed on silica gel, eluting with 10% ethyl acetate/hexane to give 2.86 g (43%) of 2-sec.-butyl-N,N-diethylbenzamide as a yellow oil.

Following a procedure similar to that described in Preparation 5 above, the latter (10.45 g, 0.045 mol), dissolved in 70 ml THF, was added to a solution of 39.2 ml (0.047 mol) of a 1.2 M solution of s-butyl lithium in cyclohexane and 7.1 ml (0.047 mol) TMEDA in 250 ml THF while maintaining the temperature at -78°C. When addition was complete the mixture was stirred for an additional one half hour at -78°C and

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then treated with sulfur dioxide at -70°C and then allowed to warm to room temperature. The mixture was taken to dryness in vacuo, and the residue was dissolved in water and added with stirring to a cold solution of 15.2 g (0.134 mol) of hydroxyl-amine-O-sulfonic acid and 15.4 ml (0.134 mol) 35% sodium hydroxide to give 10.1 g (72%) of 2-aminosulfonyl-6-sec.-butyl-N,N-diethyl-benzamide.

The latter (6.83 g, 0.22 mol) was dissolved in 100 ml glacial acetic acid and the solution heated under reflux for thirteen hours and then taken to dryness. The residue was triturated with diethyl ether and collected by filtration to give 5.7 g (83%) of the diethylammonium salt of 4-sec.-butylsaccharin.

The latter (3.0 g, 0.0096 mol), on reaction with 1.13 ml (0.012 mol) chloromethyl phenyl sulfide in toluene, afforded 3.47 g (100%) of 2-phenylthiomethyl-4-sec.-butylsaccharin.

Reaction of the latter (3.2 g, 0.0097 mol) with 2.3 ml (0.029 mol) sulfuryl chloride in 20 ml MDC afforded 2.4 g (87%) of the desired product.

6B. Preparation of 2-chloromethyl-5,6-dimethoxy-4-propylsaccharin.[IV; R^4=Pr; R^5=5-MeO,6-MeO; X=Cl]

By a procedure analogous to that described for Preparation 6A, 9.2 g (32.9 mmol) 3,4,dimethoxy-2-propyl-N,N-diethylbenzamide [V] was reacted with sulfur dioxide and 5.6 g (49.4 mmol) hydroxylamine-O-sulfonic acid to provide 7.4 g (63%) of 2-amino-sulfonyl-4,5-dimethoxy-6-propyl-N,N-dimethylbenzamide which was cyclized in quantitative yield in acetic acid and phenylthiomethylated with 1.42 ml(15 mmol) of chloromethyl phenyl sulfide to provide 4.07 g of 5,6-dimethoxy-2-phenylthiomethyl-4-propylsaccharin. Reaction of 3.59 g (8.8 mmol) of the phenylthioether with 2.12 ml (26.4 mmol) sulfuryl chloride provided 2.84 g (97%) of the desired product.

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The 3,4-dimethoxy-2-propyl-N,N-diethylbenzamide was obtained by the following procedure:

To a solution of 0.216 moles n-butyllithium in 250 ml ether at ambient temperature was added dropwise 138.2 g (0.216 mol) veratrol in 100 ml ether and 32.6 ml (0.216 mol) of TMEDA. The reaction was stirred at ambient temperature 14 hours and 21.9 ml (0.225 mol) of n-propyl iodide was added with cooling. The reaction was stirred 1 hour at RT and worked up with aqueous 1N HCl to give 14 g (36%) of 2,3-dimethoxybenzenepropane which was brominated with 14.52 g (81.6 mmol) of N-bromosuccinimide on 36 g Kieselgel in 400 ml CCl_4 according to the method of Hisatoshi et al. [Bull. Chem. Soc. Jap.32, 591-593 (1989)] to give 19.6 g (98%) of 6-bromo-2,3-dimethoxybenzenepropropane.

The bromobenzene (14.2g, 54.8 mmol) was dissolved in 200 ml ether, cooled to -78°, and 25.2 ml (63 mmol) of 2.5 N n-butyllithium in hexane was added. The reaction was warmed to 0°, held for an hour, and cooled to -70°, and 9 ml (71.2 mmol) diethyl carbamyl chloride was added. The reaction was allowed to come to RT and was quenched with saturated ammonium chloride. After extraction and drying, the product was crystallized from hexane to provide 9.5 g (62%) of 3,4-dimethoxy-2-propyl-N,N-diethylbenzamide, mp 65-67°.

6C Preparation of 2-chloromethyl-5,6-dimethoxy-4-isopropylsaccharin [IV; R^4=iPr; R^5=5-MeO,6-MeO; X=Cl]

By a process analogous to that of Preparation 6B, 10.75 g (30 mmol) 6-aminosulfonyl-3,4-dimethoxy-2-isopropyl-N,N-diethylbenzamide [V] was cyclized to provide 6.43 g of 5,6-dimethoxy-4-isopropyl saccharin (mp 186-188 from ether-hexane), 5 g (17.5 mmol) of which was phenylthiomethylated with 2.48 ml (26.3 mmol) of phenylthiomethylchloride according to the procedure of Preparation 5, and chlorinated with 3 equivalents of sulfuryl chloride to

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provide an 85% yield of the desired product, mp 117-119° from ethyl acetate-hexane.

The requisite benzamide was obtained from 2,3-dimethoxy-alpha-methylbenzeneethane by bromination followed by carbamylation as in Preparation 6B, to provide the intermediate 3,4-dimethoxy-2-isopropyl-N,N-diethylbenzamide. A solution of 66 ml 0.96M sec-butyllithium was added to 16.1 g (57.6 mmol) of the benzamide in 400 ml THF at -78° under nitrogen. After stirring 2 hours the orange anion was cannulated into excess sulfur dioxide at -60°. The reaction was allowed to come to room temperature and stirred for 18 hrs to remove SO_2. Ten ml sulfuryl chloride was added at 0° and the reaction was stripped. The sulfonyl chloride was extracted into EtOAc-ether, washed with water, dried and stripped. The residue was dissolved in 80 ml THF and 17 ml conc. NH_4OH was added at 0°. The reaction was stirred briefly at RT, stripped, and triturated in 2:1 ether-hexane to provide 12.89 g (62%) of 6-amino-sulfonyl-3,4-dimethoxy-2-iso-propyl-N,N-diethyl-benzamide, mp 138-140°.

7. Preparation of 2-chloromethyl-4-(3-pentyl)saccharin [IV; R^4=3-pentyl; R^5=H; X=Cl]

To a solution of 9.3 ml (0.058 mol) TMEDA in 340 ml THF at -78°C was added 52 ml 1.1 M solution (0.057 mol) s-butyl lithium in cyclohexane. The solution was then treated with a solution of 11.37 g (0.052 mol) 2-propyl-N,N-diethylbenzamide [V] in 75 ml THF at -78°C and the solution stirred for fifteen minutes and then treated with a solution of 8.3 ml (0.104 mol) ethyl iodide in THF. The solution was stirred for an hour and a half at -78°C and then quenched by the addition of saturated ammonium chloride added dropwise at -78°C. The mixture was then allowed to warm to ambient temperature, diluted with diethyl ether, washed first with dilute hydrochloric acid, then with water, then

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with saturated sodium bicarbonate, then with brine, dried and taken to dryness to give 12.91 g of crude product which was chromatographed on silica gel, eluting with 10% ethyl acetate/hexane to give 3.23 g (25%) of 2-(3-pentyl)-N,N-diethylbenzamide [V] as a yellow oil.

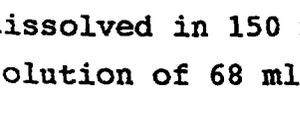
Following a procedure similar to that described in Preparation 5 above, the latter (3.05 g, 0.0115 mol) in THF was reacted with 10.5 ml (0.126 mol) 1.2 M solution of s-butyl lithium in cyclohexane in the presence of 2.1 ml (0.014 mol) of TMEDA. The resulting lithium salt was then reacted first with sulfur dioxide and then with sodium hydroxylamine-O-sulfonate to give 1.97 g (52%) of 2-aminosulfonyl-6-(3-pentyl)-N,N-diethylbenzamide as pale yellow crystals, mp 118-120°C (soft 102°), 1.84 g (0.0056 mol) of which was cyclized in 22 ml refluxing glacial acetic acid to give 1.28 g (70%) of the diethylammonium salt of 4-(3-pentyl)saccharin, [II], mp 107.5-109.5°C.

The latter (0.0037 mol), on reaction with 0.74 ml (0.0055 mol) chloromethyl phenyl sulfide in the presence of 116 mg (0.0004 mol) TBAB in 45 ml toluene, afforded 1.93 g of 2-phenylthiomethyl-4-(3-pentyl)-saccharin as a pale yellow oil, 1.93 g (0.0037 mol) of which, on reaction with 0.59 ml (0.0073 mol) of sulfuryl chloride in 37 ml MDC, afforded 1.2 g of the desired product as a pale yellow oil.

8. Preparation of 2-chloromethyl-4,6-dimethoxysaccharin [IV; R^4=MeO; R^5=6-MeO; X=Cl]

A solution of 50.0 g (0.27 mol) of 2,4-dimethoxybenzoic acid in 60 ml (98.0 g, 0.82 mol) thionyl chloride was heated under reflux for three hours, then cooled, and the excess thionyl chloride distilled off. The resulting 2,4-dimethoxybenzoyl chloride was dissolved in 150 ml MDC and the solution treated with a solution of 68 ml (48 g, 0.66 mol) diethylamine in

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500 ml MDC, cooled to 0°C. When addition was complete the mixture was stirred for fifteen hours at ambient temperature, then washed with saturated sodium bicarbonate, water and brine and taken to dryness and the residue distilled in vacuo to give 44.78 g (69%) of 2,4-dimethoxy-N,N-diethylbenzamide [V], b.p.155-163°C-/0.4 mm.

Following a procedure similar to that described in Preparation 5 above, 10.0 g (0.042 mol) of the product in 250 ml THF was reacted with 40.57 ml 1.1 M solution (0.044 mol) s-butyl lithium in cyclohexane and 6.35 ml (0.042 mol) of TMEDA in THF. The resulting lithium salt was then reacted first with about 40 ml sulfur dioxide and then with an aqueous solution (0.13 mol) of sodium hydroxylamine-O-sulfonate to give 8.26 g of 2-aminosulfonyl-4,6-dimethoxy-N,N-diethylbenzamide, 7.0 g of which (0.022 mol) was cyclized in 80 ml refluxing glacial acetic acid to give 6.6 g (94%) of the diethylammonium salt of 4,6-dimethoxysaccharin [II] which was used as such in the next step without further purification.

The latter (6.0 g, 0.019 mol), on reaction with 3.82 ml (0.028 mol) chloromethyl phenyl sulfide in the presence of 0.611 g (0.0019 mol) of TBAB in 200 ml toluene, afforded 6.2 g (89%) of 2-phenylthiomethyl-4,6-dimethoxysaccharin, 5.82 g of which (0.016 mol), on reaction with 3.23 g (0.0019 mol) sulfuryl chloride in 100 ml MDC, afforded 4.63 g (100%) of the desired product, m.p. 185-187°C.

9A-9G Preparation of 2-halomethyl-4-R^4-R^5-saccharins

Following a procedure similar to that described above in Preparation 5, substituting for the 2-methoxy-N,N-diethylbenzamide [V] used therein an appropriate 2-R^4-R^5-substituted-N,N-diethylbenzamide, the following 2-halomethyl-4-R^4-R^5-saccharins listed in TABLE A were prepared via the corresponding 2-phenyl-

thiomethylsaccharins. Wherever available, the melting point, recrystallization solvent and yield are given for each of the 2-unsubstituted saccharins, the 2-phenylthiomethylsaccharins and the 2-chloromethylsaccharins in columns headed "mp/Solv." and "Yield". In all instances, the intermediate 2-phenylthiomethylsaccharins were used directly in the subsequent step without further characterization or purification.

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TABLE A

Prep	R^4/R^5	Sacc		$2\text{-}C_6H_5SCH_2\text{-}Sacc$		$2\text{-}ClCH_2\text{-}Sacc$	
		mp/Solv	Yield	mp/Solv	Yield	mp/Solv	Yield
9A	H 7-Cl	260-262	93	--	100	158.0-160.0 i-PrOH	51
9B	$CH(CH_3)_2$ H	177.0-178.0 MeOH	88	--	100	93.0-96.0 i-PrOH-Cyc.hex	100
9C	CH_3O $5\text{-}CH_3O$	(a)	64	--	100	190.0-192.0	76
9D	$COOCH_3$ H	(b) EtOAc-hex	76	--	65	186.0-187.0	
9E	C_2H_5O H	(a)	96	--	95	139.0-140.0	97
9F	$(CH_3)_2CHO$ H		87	--	75	142.5-143.5	94
9G	C_2H_5 $5,7\text{-}(CH_3O)_2$	i-PrOH	67	--	52	--	99

(a) Isolated and used in the next step as the diethylammonium salt.
(b) The 2-unsubstituted-saccharin was prepared by cyclization of dimethyl 3-aminosulfonylphthalate in methanol in the presence of a molar equivalent of sodium methoxide. The phthalate ester was prepared by diazotization of dimethyl 3-aminophthalate, decomposition of the diazonium salt with sulfur dioxide in the presence of cupric chloride and reaction of the resulting dimethyl 2-chlorosulfonylphthalate with ammonia. (84% yield overall).

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10. Preparation of 2-bromomethylsaccharin [IV; R^4=H; R^5=H; X=Br]

Following a procedure similar to that described in Preparation 2, reaction of 18.3 g (0.1 mol) of saccharin with 70 ml 37% formalin in ethanol afforded 3.58 g (70%) of 2-hydroxymethylsaccharin [III]. The latter (25 g, 0.117 mol) was reacted with 63.3 g (0.234 mol) phosphorus tribromide in diethyl ether to give 29.8 g (92%) of the desired product, mp 155-157°C.

11. Preparation of 2-chloromethyl-6-nitrosaccharin [IV; R^4=H; R^5=6-NO_2; X=Cl]

To a solution of 4 g (0.0175 mol) 6-nitrosaccharin [II] in 240 ml ethanol was added 4.4 g (0.0175 mol) thallium ethoxide, and the mixture was allowed to stand at room temperature for one hour, cooled for about 16 hours and the precipitated solid collected and dried to give 7.6 g (100%) of the thallium salt of 6-nitrosaccharin. The product was suspended in 50 ml DMF and the mixture treated with 3.07 g (0.0194 mol) chloromethyl phenyl sulfide, the mixture warmed at about 63°C for five hours, allowed to stand at ambient temperature for about 16 hours, and then poured into ice water. The crude product, obtained by filtration, was stirred in MDC and filtered to remove thallium salts. The filtrate was freed of solvent, and the resultant pale yellow solid was sonicated with warm ethanol and once again collected and dried to give 4.6 g (75%) of 6-nitro-2-phenylthiomethylsaccharin, mp 161-163°C. The latter, on reaction with sulfuryl chloride in MDC using the procedure described above in Preparation 4, afforded 3.7 g of the desired product.

12 Preparation of 2-chloromethyl-5-(1,1,3,3-tetramethylbutyl)saccharin.[IV; R^4=H; R^5=5-(1,1,3,3-tetra-MeBu; X=Cl]]

A solution of 49.8 g (0.199 mol) of 2-hydroxy-5-(1,1,3,3-tetramethylbutyl)benzoic acid in

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200 ml methanol was heated to 50°C and then treated dropwise with about 80 g sulfuric acid at a rate to maintain the reaction under reflux. The reaction mixture was heated under reflux for an additional 11 hours, then cooled and partitioned between water and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, then with brine, dried over sodium sulfate and taken to dryness to give 48.6 g (92%) of methyl 2-hydroxy-5-(1,1,3,3-tetramethylbutyl)benzoate.

The latter dissolved in 250 ml DMF was treated first with 40.4 g (0.36 mol) of 1,4-diazabicyclo[2.2.2]octane followed by 33.4 g (0.27 mol) N,N-dimethylchlorothiocarbamate and 100 ml DMF. The reaction mixture was heated at 45°C for about eight hours, cooled, poured into ice/water and concentrated hydrochloric acid and then extracted with ethyl acetate. The combined organic extracts were washed with dilute hydrochloric acid, then with sodium bicarbonate and then with brine, dried and taken to dryness to give 48.2 g (76%) of methyl 2-(N,N-dimethylthiocarbamyloxy)-5-(1,1,3,3-tetramethylbutyl)benzoate which was heated at 220°C for 15 hours, then cooled, dissolved in toluene and chromatographed on silica, eluting with 1:9 ethyl acetate:toluene, to give 3.6 g (14%) of methyl 2-(N,N-dimethylcarbamylthio)-5-(1,1,3,3-tetramethylbutyl)benzoate.

A solution of the latter (0.025 mol) in 40 ml MDC was treated, with stirring, with 80 ml glacial acetic acid, followed by 16 ml water. The reaction mixture was cooled to 0°C, and chlorine was bubbled through the reaction mixture for about five minutes while maintaining the temperature between 5 and 24°C. The reaction was stirred for an additional 30 minutes, concentrated in vacuo, and the remaining solution poured into ice water. Extraction of the mixture with ethyl

acetate and isolation of the product from the combined organic extracts afforded 6.8 g (78%) of methyl 2-chlorosulfonyl-5-(1,1,3,3-tetramethylbutyl)benzoate.

The product (9.0 g, 0.026 mol) was dissolved in THF and added to 100 ml concentrated ammonium hydroxide with cooling in an ice bath. The resulting solution was stirred for about 16 hours, then concentrated in vacuo and the concentrated solution acidified to pH 3 with concentrated hydrochloric acid. The mixture was stirred for several hours, and the separated solid collected, washed with water and dried to give 9.0 g of 5-(1,1,3,3-tetramethylbutyl)-saccharin [II], mp 213-215°C.

Following a procedure similar to that described in Preparation 11, 9.0 g (0.30 mol) of the product was reacted with thallium ethoxide in ethanol and the resulting thallium salt reacted with 3.33 g (0.021 mol) of chloromethyl phenylsulfide in DMF to give 5.76 g (66%) of 2-phenylthiomethyl-5-(1,1,3,3-tetramethylbutyl)saccharin, 3.3 g (0.007 mol) of which was treated with 0.944 g sulfuryl chloride in MDC to give 1 g (41%) of the desired product.

13. Preparation of 2-chloromethyl-4-methylsaccharin. [IV; R^4=Me; R^5=H; X=Cl]

Following a procedure similar to that described in Preparation 12 above, 15.5 g (0.086 mol) ethyl 2-hydroxy-6-methylbenzoate was reacted with 15.9 g (0.129 mol) N,N-dimethylchlorothiocarbamate in the presence of 19.3 g (0.172 mol) of 1,4-diazabicyclo-[2.2.2]octane in DMF to give 22.1 g (96%) of ethyl 2-(N,N-dimethylthiocarbamyloxy)-6-methylbenzoate which was heated at 220°C for about 10 hours. The product was purified by chromatography on silica gel in MDC to give ethyl 2-(N,N-dimethylcarbamylthio)-6-methylbenzoate as a red-brown oil.

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A solution of the latter (22.6 g, 0.0844 mol) in 170 ml MDC was treated with 340 ml glacial acetic acid and 68 ml water while cooling in an ice/acetone bath, and chlorine was bubbled through the reaction mixture for 10-15 minutes.The reaction vessel was evacuated to remove excess chlorine and MDC and the mixture poured into water and partitioned between MDC and water. The organic layer, on drying and evaporation to dryness, afforded 19 g of ethyl 2-chlorosulfonyl-6-methylbenzoate, 5 g (0.019 mol) of which was reacted with concentrated ammonium hydroxide in THF to give 6.1 g (67%) of 4-methylsaccharin [II].

Following a procedure similar to that described in Preparation 11 above, the product (10.1 g, 0.0512 mol) was converted to the thallium salt by reaction with 12.8 g (0.0512 mol) of thallium ethoxide in ethanol and the thallium salt reacted with 6.7 g (0.0427 mol) of chloromethyl phenyl sulfide in DMF to give 6.85 g (50%) of 2-phenylthiomethyl-4-methyl-saccharin.

Reaction of the latter (6.7 g, 0.021 mol) with sulfuryl chloride in MDC afforded 4.9 g (95%) of the desired product.

14A. Preparation of 2-chloromethyl-4,7-dimethoxy-saccharin [IV; R^4=MeO; R^5=7-MeO; X=Cl]

A mixture of 75 g (0.36 mol) 3,3-dithiobis-propionic acid, 102 ml thionyl chloride and a catalytic amount of pyridine was stirred for about 24 hours and then evaporated to dryness in vacuo. The residue was treated with MDC and evaporated to dryness again to remove residual thionyl chloride and pyridine to give 87 g (98%) of the corresponding bis acid chloride, 44.8 g (0.18 mol) of which was dissolved in THF and added dropwise to a solution of 77.16 g (0.72 mol) benzylamine in THF. The mixture was stirred for two

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hours at 40-45°C, cooled and the precipitated solid collected, washed with water and dried to give 59 g (84%) of 3,3-dithiobispropionic acid N,N'-dibenzylcarboxamide, mp 162-165°C.

Reaction of 7.0 g (0.018 mol) of the latter with 10.25 g (0.076 mol) sulfuryl chloride in MDC gave a mixture of 2-benzyl-2H-isothiazol-3-one and 5-chloro-2-benzyl-2H-isothiazol-3-one which were largely separated from one another by sonication in MDC (which solubilized most of the former). The insoluble material was collected by filtration and chromatographed on silica gel with MDC. There was thus obtained 5-chloro-2-benzyl-2H-isothiazol-3-one, mp 58-68°C.

A solution of 10 g (0.044 mol) of the latter in MDC was cooled to 0°C and the solution treated with 7.6 g (0.044 mol) 3-chloroperbenzoic acid, the mixture stirred for 10 minutes and then treated with a second 7.6 g portion of the perbenzoic acid. The reaction mixture was filtered, the filter washed with MDC and the filtrate washed with saturated sodium bicarbonate, then with brine, dried over sodium sulfate and taken to dryness and the residue chromatographed in MDC on silica gel, the product being eluted with 50:50 hexane:MDC, to give 7.15 g (46%) of 5-chloro-2-benzyl-2H-isothiazol-3-one-1-oxide.

A solution of 1.1 g (0.0045 mol) of the latter in 8 ml benzene was treated with 0.55 g (0.0051 mol) of 2-methoxyfuran and the solution heated in a pressure bottle at 70°C for 1.5 hours and then cooled and the solid collected, washed with benzene and dried to give 2-benzyl-7-hydroxy-4-methoxybenziso-thiazol-3-one-1-oxide, mp 235-237°C.

A mixture of the product (1.85 g, 0.006 mol), 2.48 g (0.018 mol) of potassium carbonate and 1.70 g (0.012 mol) of methyl iodide in acetone was heated under reflux for 1.5 hours and then cooled and poured into

water. The solid which separated was collected by filtration, washed with water and dried to give 1.70 g (89%) of 2-benzyl-4,7-dimethoxybenzisothiazol-3-one-1-oxide, 1.13 g (0.0035 mol) of which was oxidized with 1.20 g (0.007 mol) of 3-chloroperbenzoic acid in MDC using the procedure described above to give 1.03 g (88%) of 2-benzyl-4,7-dimethoxysaccharin.

A mixture of 2.07 g (0.0062 mol) of the product, 1.37 g (0.02 mol) of ammonium formate and 1.5 g of 10% palladium-on-charcoal catalyst in 80 ml methanol was heated under reflux for one hour, then cooled and filtered, and the filtrate taken to dryness to give 0.92 g (57%) of the ammonium salt of 4,7-dimethoxysaccharin [II].

A solution of 1.11 g (0.0042 mol) of the ammonium salt was dissolved in DMF, 0.67 g (0.0042 mol) of chloromethyl phenyl sulfide was added, and the solution heated under reflux for eight hours and then cooled and poured into ice water.The solid which separated was collected, washed with water and dried to give 0.50 g (33%) of 2-phenylthiomethyl-4,7-dimethoxy-saccharin.

Reaction of the latter (0.5 g, 0.0013 mol) with sulfuryl chloride in MDC using the procedure described above in Preparation 4 afforded 0.22 g (58%) of the desired product.

14B and 14C. Preparation of 2-chloromethylsaccharins

Following a procedure similar to that described in Preparation 14A, other 2-chloromethyl-saccharin derivatives were prepared as follows:

14B. Preparation of 2-chloromethyl-4-ethoxy-7-[2-(2-methoxyethoxy)ethoxy]saccharin

[IV; R^4=EtO; R^5=7-[2-(2-MeOEtO)C_2H_4O; X=Cl]

Reaction of 5.8 g (0.024 mol) 5-chloro-2-benzyl-2H-isothiazol-3-one-1-oxide with 3.76 g (0.0335 mol) 2-ethoxyfuran afforded 3.05 g (40%) of

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2-benzyl-4-ethoxy-7-hydroxybenzisothiazol-3-one-1-oxide, 5.7 g of which was reacted with 3.6 g (0.0197 mol) 2-[2-methoxyethoxy]ethyl bromide in the presence of 4.95 g (0.0358 mol) potassium carbonate in 125 ml methyl ethyl ketone and 25 ml DMF to give 7.0 g (93%) of 2-benzyl-4-ethoxy-7-[2-(2-methoxyethoxy)ethoxy]benzisothiazol-3-one-1-oxide, which was oxidized as before with 3-chloroperbenzoic acid in MDC to give 2-benzyl-4-ethoxy-7-[2-(2-methoxyethoxy)ethoxy]saccharin. Debenzylation of 6.6 g (0.015 mol) of the latter with 3.34 g (0.053 mol) ammonium formate in the presence of 6.4 g 10% palladium-on-charcoal catalyst in methanol afforded the ammonium salt of 4-ethoxy-7-[2-(2-methoxyethoxy)ethoxy]saccharin [II] which was reacted with 2.38 g (0.015 mol) of chloromethyl phenyl sulfide in 100 ml DMF to give 1.46 g (21%) of 2-phenylthiomethyl-4-ethoxy-7-[2-(2-methoxyethoxy)ethoxy]saccharin, mp 73-75°C (from isopropanol). Treatment of 1.4 g (0.0029 mol) of the product with 0.4 g (0.0029 mol) sulfuryl chloride in MDC afforded 1.16 g (100%) of the desired product.

14C. Preparation of 2-chloromethyl-4-methoxy-7-[2-(2-methoxyethoxy)ethoxy]saccharin

[IV; R^4=MeO; R^5=7-[2-(2-MeOEtO)CCH_2O; X=Cl]

Reaction of 3.03 g (0.01 mol) 2-benzyl-7-hydroxy-4-methoxybenzisothiazol-3-one-1-oxide (Preparation 14A) with 2.01 g (0.011 mol) 2-(2-methoxyethoxy)ethyl bromide in methyl ethyl ketone in the presence of 2 g (0.015 mol) potassium carbonate afforded 2.58 g (64%) of 2-benzyl-4-methoxy-7-[2-(2-methoxyethoxy)ethoxy]benzisothiazol-3-one-1-oxide, which, on oxidation with 1.1 g (0.0063 mol) 3-chloroperbenzoic acid in MDC, gave 2-benzyl-4-methoxy-7-[2-(2-methoxyethoxy)ethoxy]saccharin. Debenzylation of 0.25 g (0.0006 mol) of the product with 0.13 g (0.0021 mol) ammonium formate in methanol in the presence of 0.25 g

10% palladium-on-charcoal gave 0.21 g (100%) of the ammonium salt of 4-methoxy-7-[2-(2-methoxyethoxy)-ethoxy]saccharin [II]. Reaction of 1.4 g (0.004 mol) of the ammonium salt with 0.63 g (0.004 mol) chloromethyl phenyl sulfide in DMF afforded 2-phenylthiomethyl-4-methoxy-7-[2-(2-methoxyethoxy)ethoxy]saccharin, which, on reaction with sulfuryl chloride in MDC,afforded 0.53 g (35%) of the desired product.

15. Preparation of 2-fluoromethylsaccharin [IV; R^4=H; R^5=H; X=F]

A solution of 1.89 g (0.011 mol) diethylamino sulfur trifluoride (DAST) in 20 ml MDC was added to a suspension of 2.13 g (0.01 mol) 2-hydroxymethyl-saccharin [III] in 25 ml MDC while maintaining the reaction mixture at -78°C.

The reaction mixture was stirred at -78°C for one hour, the temperature allowed to slowly rise to ambient temperature, the mixture stirred for 16 hours and then poured into ice-water. The organic layer was separated and washed with water, dried over magnesium sulfate and taken to dryness to give 2.2 g of product which was recrystallized from ethyl acetate to give 1.6 g (74%) of the desired product, mp 96-98°C.

16A Preparation of 2-chloromethyl-4-ethylsaccharin. [IV; R^4=Et; R^5=H; X=Cl]

To a solution of 0.5 g (0.0025 mol) 4-methyl-saccharin [II] in THF cooled to -78°C by a dry ice/-acetone bath was added, dropwise with stirring, a solution of 5.2 ml 1.3M solution of s-butyl lithium in cyclohexane. The mixture was stirred an additional hour at -78°C and then treated with 0.16 ml (0.025 mol) methyl iodide over a 1 1/2 hour period. The mixture was stirred for an hour and 45 minutes, quenched in 25 ml 1N hydrochloric acid, the reaction mixture rendered basic, the aqueous mixture extracted with chloroform and then acidified and extracted with ethyl acetate. The

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combined organic extracts were washed with 10% sodium thiosulfate, then with brine, dried over sodium sulfate and taken to dryness to give a product, whose PMR spectrum indicated a mixture consisting of 74% of 4-ethylsaccharin and 21% of 4,7-dimethylsaccharin.

Following a procedure similar to that described in Preparation 4 above, the crude material (0.47 g, 0.0022 mol) was reacted with 0.24 ml (0.0028 mol) of chloromethyl phenylsulfide in toluene in the presence of TBAB, and the product chromatographed on silica gel, eluting with MDC, 5 ml fractions being collected. The first 420 ml of eluate were discarded. The next 20 fractions, on evaporation, afforded 0.07 g of material, predominantly 2-phenylthiomethyl-4,7-dimethylsaccharin, which was set aside. The next 25 fractions afforded 0.37 g of 2-phenylthiomethyl-4-ethylsaccharin, which was reacted with sulfuryl chloride in MDC to give 0.19 g (66%) of the desired product

16B. Preparation of 2-chloromethyl-4-propylsaccharin. [IV; R^4=Pr; R^5=H; X=Cl]

Following a procedure similar to that described in Preparation 16A, 10 g (0.051 mol) 4-methylsaccharin in THF was reacted with 86 ml (0.10 mol) of a 1.18M solution of s-butyl lithium in cyclohexane and the resulting solution treated with 4.5 ml (0.050 mol) ethyl iodide to give 10.15 g (89%) of 4-propylsaccharin [II], which, on reaction with 5.32 ml (0.056 mol) of chloromethyl phenyl sulfide in toluene in the presence of TBAB, afforded a crude mixture from which was isolated by flash chromatography on silica gel 2-phenylthiomethyl-4-propylsaccharin as an oil, 1.8 g (0.0052 mol) of which, on reaction with 1.25 ml (0.016 mol) sulfuryl chloride in MDC, afforded 0.94 g (66%) of the desired product.

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16C. Preparation of 4-ethylsaccharin [II; R^4=Et; R^5=H; X=H]

A preferred alternative to preparation 16A is as follows:

To a solution of 5.13 g (25 mmol) N,N,2-triethylbenzamide in THF (50 ml) at -78° was added a solution of LDA (Aldrich 2.0M, 15.63 ml, 31.25 mmol). The solution was warmed to -10°C with ice water over 1 hr, then cooled to -78°C with dry ice-acetone. TMSCl (6.34 ml, 50 mmol) was added neat at -78°C and then reaction brought to room temperature after 1 hr. The reaction was quenched with saturated NH_4Cl and extracted with ether (2 x 100 ml), dried over $MgSO_4$, stripped and the residue distilled in a Kugelrohr (130-140°C, 0.65 mm) to obtain 6.51 g (94%) of N,N-diethyl-2-[1-(trimethylsilyl)ethyl]benzamide.

To a solution of sec-BuLi (0.97M, 5.10 ml, 4.96 mmol) and TMEDA (0.75 ml, 4.96 mmol) in THF at -78°C was added the amide (1.25 g, 4.50 mmol) in THF. Excess SO_2 in THF was added quickly at -78°C then warmed to room temperature. The THF was removed in vacuo and the residue treated at 0°C with two equivalents of a 1:1 solution of sodium hydroxide (0.36 g, 9.0 mmol) and hydroxylamine-O-sulfonic acid (1.0 g, 9.0 mmol) in H_2O. The reaction was stirred at room temperature for 4 hrs, extracted with EtOAc, dried over $MgSO_4$, concentrated and flash chromatographed on silica gel with 20% ethyl acetate/hexane to give 0.62 g (41%) of 2-aminosulfonyl-N,N-diethyl-6-[1-(trimethylsilyl)ethyl]benzamide. The benzamide (0.95 g, 2.66 mol) was refluxed in glacial acetic acid (20 ml) for 18 hr, stripped to dryness, triturated with hot cyclohexane (30 ml) and a trace of EtOAc (3 ml), cooled with scratching and filtered. There was obtained 0.81 g (85%) of 4-[1-(trimethylsilyl)ethyl]saccharin, mp 123-125°C.

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To the trimethylsilylethylsaccharin (0.25 g, 0.70 mmol) in DMF (9 ml) at room temperature was added H_2O (1 ml) and cesium fluoride (0.75g ,4.94 mmol, 7 equivalents). After 7 hr the reaction was poured into 5% NaOH and extracted with EtOAc. The aqueous layer was acidified with 12N HCl and extracted with Et_2O-EtOAc (1:1), dried over Na_2SO_4, filtered and stripped to give a colorless solid in quantitative yield. It was recrystallized from 5% Et_2O-hexanes to give 0.091 g (64%) of the desired product, mp 183-185°C.

17. Preparation of 2-chloromethyl-4,7-dimethyl-saccharin [IV; R^4=Me; R^5=7-Me; X=Cl]

The 0.07 g sample of material obtained in the early fractions from the chromatographic separation described above in Preparation 16A consisting predominantly of 2-phenylthiomethyl-4,7-dimethyl-saccharin was reacted with 0.05 ml sulfuryl chloride in MDC and the product recrystallized from cyclohexane-ethyl acetate to give 20 mg (51%) of the desired product, mp 107-108°C.

18A. Preparation of 2-chloromethyl-4-isopropyl-6-methoxysaccharin [IV; R^4=iPr; R^5=6-MeO; X=Cl]

To a solution of 40.0 g (0.174 mol) 2-isopropyl-4-methoxybromobenzene in 600 ml diethyl ether at 0°C was added 103.68 ml (0.175 mol) 1.69M solution of butyl lithium in diethyl ether. When the addition was complete the solution was cooled to 0°C for one hour and stirred for an additional five hours at ambient temperature, then recooled to -78°C and treated with a solution of 23.68 g (0.175 mol) N,N-diethylcarbamyl chloride in 80 ml diethyl ether. The resulting solution was stirred for about 12 hours while the reaction temperature was allowed to rise and then quenched with saturated ammonium chloride solution. The aqueous and organic layers were separated, the aqueous layer back extracted with ethyl acetate and the combined organic

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extracts washed once with brine, then dried and the solution taken to dryness to give a crude product which was flash chromatographed on silica gel, eluting with 30% ethyl acetate/hexane to give 34.4 g (79%) of 2-isopropyl-4-methoxy-N,N-diethylbenzamide [V] as an oil which was used as such in the next step without further purification. The oil can be distilled, if desired, and boils at 123-129/0.2-0.3 mm.

Following a procedure similar to that described in Preparation 5 above, the latter (15.0 g, 0.060 mol) in 100 ml diethyl ether was reacted with 77.8 ml (0.784 mol) 1.2M solution of s-butyl lithium in cyclohexane in the presence of 6.98 g (0.06 mol) TMEDA. The resulting lithium salt was then reacted first with 50 ml sulfur dioxide and then with 0.181 mol sodium hydroxylamine-O-sulfonate to give 11.6 g (59%) of 2-aminosulfonyl-6-isopropyl-4-methoxy-N,N-diethyl-benzamide, m.p. 103-105°C (from ethyl acetate/hexane). 11.0 g, 0.034 mol) of the benzamide was cyclized in 200 ml refluxing glacial acetic acid to give 10.3 g of the diethylammonium salt of 4-isopropyl-6-methoxysaccharin, [II] m.p. 132-135°C.

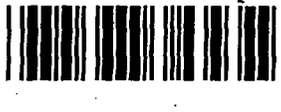
The latter (0.030 mol), on reaction with 6.14 ml (7.25 g, 0.046 mol) chloromethyl phenyl sulfide in the presence of 0.98 g (0.003 mol) of TBAB in 250 ml toluene, afforded 10.1 g (88%) of 2-phenylthiomethyl-4-isopropyl-6-methoxysaccharin as an oil, 9.7 g (0.026 mol) of which, on reaction with 3.1 ml (5.21 g, 0.039 mol) sulfuryl chloride in MDC, afforded 6.9 g (88%) of the desired product, mp 151-152°C.

18B Preparation of 2-chloromethyl-4-isopropyl-6-methoxysaccharin [IV; R^4=iPr; R^5=6-MeO; X=Cl]

An alternative procedure was also followed:

To a solution of 300 ml TMEDA (1.99 moles) in 4 l anhydrous ether was added 1550 ml sec-BuLi (1.3 M)

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and the system was cooled to -70°C under a nitrogen atmosphere. A solution of 454.2 g 2-isopropyl-4-methoxy N,N-diethylbenzamide [V] (1.82 moles) in 300 ml anhydrous ether was added dropwise over 30 minutes (the temperature was maintained at or below -60°C during the addition). After the addition was complete, the reaction was stirred at -70°C for one hour and allowed to warm to -50°C. After holding the temperature at -50°C for 30 minutes, the mixture was cooled back to -70°C. To this stirred solution was added via cannulating tube a solution of 200 g SO_2 in 200 ml dry ether precooled to -40°C under positive nitrogen pressure over a 20-minute period. The temperature of the reaction mixture during the addition was maintained below -40°C. (A white powdery precipitate of aryl lithium sulphinate separated out almost immediately). After the addition, the ice-bath was removed and the reaction was allowed to stir at ambient temperature for two hours. It was cooled to -5°C and to this stirred solution was added 190 ml sulfuryl chloride (2.36 moles) dropwise over a 15-minute period maintaining the temperature below 10°C during the addition. After further stirring for 30 minutes at 0-5°C, a white insoluble precipitate was filtered off and washed with 2 l anhydrous ether. Removal of the solvent at atmospheric pressure afforded the sulfonyl chloride as a crude dark oil. This crude sulfonyl chloride was dissolved in 1.4 l THF, cooled to -10°C, and 540 ml concentrated NH_4OH (28%) was added in portions over 15 minutes (the temperature was kept at 15°C or below throughout the addition). After stirring for 15 minutes at ambient temperature, the THF and excess ammonia were removed under vacuum to give a dark oil, which was diluted with 6.0 water and acidified with 3N HCl to pH 1. The light yellow solid was collected by filtration and washed with 800 ml water. The solid was

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dried at 60°C under vacuum for 18 hours and recrystallized from a mixture of 800 ml ethyl acetate and 3 l hexane to give 429 g (72%) of 2-aminosulfonyl-6-isopropyl-4-methoxy-N,N-diethylbenzamide, mp 122-125°C.

A solution of 429.6 g of the diethylbenzamide (1.31 mole) in 1.5 l acetic acid was refluxed for 20 hours. It was cooled to room temperature and the solvent removed under vacuum. The oily residue was dissolved in 6 l water and adjusted to pH 1 with 6N HCl. The crude product was collected by filtration and washed with 2 l water. The solid was dried at 60°C under vacuum for 18 hours and recrystallized from ethyl acetate/hexane to give 303 g (91%) 4-isopropyl-6-methoxysaccharin [II], mp 188°C.

To a suspension of 24 g paraformaldehyde (0.8 mole) and 86.4 g chlorotrimethylsilane (1.6 moles) in 200 ml 1,2-dichloroethane was added 0.8 ml anhydrous tin(IV) chloride and the resulting solution stirred on a steam bath for one hour. At the end of this period, 51 g 4-isopropyl-6-methoxysaccharin (0.2 mole) was added to the clear solution and the reaction mixture was further refluxed for 18 hours. It was cooled to room temperature, poured into water, the organic layer separated and washed with 50 ml 2N sodium hydroxide solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated under vacuum to give crude product. It was purified by crystallization from ethyl acetate/hexane to give 57 g (87%) of the desired product, mp 151°C.

19. Preparation of 2-chloromethyl-4-isopropyl-6-hydroxysaccharin [IV; R^4=iPr; R^5=6-OH; X=Cl]

To a solution of 1.0 g (0.0039 mol) of 4-isopropyl-6-methoxysaccharin in 15 ml MDC was added at ambient temperature 1.28 g (5.12 ml) of a 1 M solution of boron tribromide in MDC. When addition was complete

the reaction mixture was heated under reflux for about five hours, cooled, taken to dryness in vacuo and the residue treated with ice and saturated sodium bicarbonate. The aqueous solution was extracted once with ethyl acetate and then acidified to pH 1 with concentrated hydrochloric acid. Extraction of the mixture with ethyl acetate/diethyl ether (8:2), drying the organic extracts and removal of the solvent in vacuo afforded 0.9 g (96%) of 6-hydroxy-4-isopropylsaccharin as a white crystalline solid which was used as such in the next step.

An alternative procedure was also used. To a stirred suspension of 62.74 g (0.47 mol) $AlCl_3$ in 500 ml chloroform at 0° was added 43.9 g (0.7 mol) of ethanethiol. Within minutes a clear solution formed. To this a solution of 20.0 g (0.078 mol) 4-isopropyl-6-methoxysaccharin in 550 ml chloroform was added over a 30-min period. This solution was allowed to warm to RT and stirred for 3-4 hr at 60°. After cooling, the mixture was poured into ice-water and acidified with dilute HCl. The solid which separated was collected by filtration, washed with water and dried to give 18.4 g (97%) of 6-hydroxy-4-isopropylsaccharin [II].

Following a procedure similar to that described in Preparation 4 above, the latter (0.004 mol) was reacted with 0.61 ml (0.0046 mol) chloromethyl phenyl sulfide in toluene in the presence of 0.133 g (0.004 mol) TBAB to give 0.32 g (21%) of 4-isopropyl-6-hydroxy-2-phenylthiomethylsaccharin, m.p. 127-129.5, 1.78 g of which was treated with 0.43 ml (0.73 g) sulfuryl chloride in MDC to give 1.2 g (84%) of the desired product, m.p. 149-150°C.

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22. Preparation of 2-chloromethyl-4-isopropyl-6-hydroxysaccharin [IV; R^4=iPr; R^5=6-OH; X=Cl]

5g (0.0207 mol) 6-hydroxy-4-isopropyl-saccharin was dissolved in 150 ml methanol and 3.4 g (0.0104 mol) Cs_2CO_3 was added. The mixture was stirred for 3-4 hr at RT. The excess methanol was removed under reduced pressure and the residue was dried for 2 hr under high vacuum. The residue was then dissolved in 110 ml DMF and 0.32 g (0.0209 mol) chloromethyl phenyl sulfide was added. The stirred mixture was heated at 70-75° for 12 hr, cooled, treated with ice water and extracted with 600 ml 4:1 ethyl acetate:ether. The organic layer was washed with water and saturated NaCl and dried. The solvent was removed under reduced pressure. The residue was purified by flash chromatography with 20% ether in MDC. There was obtained 4.5 g (60%) of 4-isopropyl-6-hydroxy-2-phenyl-thiomethylsaccharin, mp 150-151.5°C which, on reaction with sulfuryl chloride as described in Preparation 19, yielded the desired product as before.

23. Preparation of 2-chloromethyl-4-isopropyl-6-dimethylamino-7-chlorosaccharin

[IV; R^4=iPr; R^5=6-diNMe_2,7-Cl; X=Cl}

To a solution of 5-chloro-2-benzyl-4-isothiazolin-3-one (J. Het. Chem. 8, 571, 1971) (9.4 g, 0.04 mol) in MDC (100 ml) was added in one portion 80-85% 3-chloroperoxybenzoic acid (10.8 g, 0.06 mol) and the resulting mixture stirred at room temperature overnight under nitrogen. The precipitated solids were filtered off and washed with MDC (50 ml). The combined filtrate was evaporated to near dryness and the residue partitioned between ethyl acetate (300 ml) and saturated $NaHCO_3$ (100 ml). The layers were separated and the organic phase washed with saturated $NaHCO_3$ (2 x 100 ml), brine (1 x 100 ml) and dried. Removal of the solvent in vacuo afforded 10.0 g (99%) of 5-chloro-2-benzyl-

4-isothiazolin-3(2H)-one 1-oxide as a pale yellow oil.

The 1-oxide (10.0 g, 0.04 mol) in glacial acetic acid (200 ml) was treated with 30% H_2O_2 (100 ml, 0.88 mol) and heated on a steam bath for 2 hr during which time an additional 30 ml (0.26 mol) 30% H_2O_2 was added. After heating on a steam bath for an additional hour, the reaction mixture was cooled to room temperature and poured into ice cold water (1 l) and stirred. The precipitated solids were collected by filtration, washed with water (2 x 100 ml), hexanes and air dried to give 4.8 g (45%) of 5-chloro-2-benzyl-4-isothiazolin-3(2H)-one 1,1-dioxide as a colorless solid.

The dioxide (1.2 g 4.7 mmol) was mixed with 2.02 (11 mmol) 2-trimethylsiloxy-5-methylhexa-1,3-diene (prepared from 5-methylhex-3-ene according to the method of E.J. Corey et al., Tet. Lett. 495, 1984) in toluene (50 ml) and refluxed for a period of 20 hr under nitrogen. The resulting mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in THF (25 ml) and treated with 2N HCl (10 ml). After stirring under nitrogen at room temperature for 10 min, ether (100 ml) was added and the layers separated. The organic phase was washed with water, brine, dried and evaporated to dryness to give a pale yellow foam. The foam was dissolved in toluene (30 ml), DBN (1.5 ml) was added and stirred at room temperature for 2 hr. MDC (100 ml) and 2N HCl (50 ml) were added and stirring continued for 5 min. The layers were separated and the organic phase washed with water, brine and dried. Removal of the solvent in vacuo and purification of the residue by flash chromatography on silica gel (5:4:1, hexanes:MDC:ether) gave 0.6 g (39%) of 2-benzyl-4-isopropyl-6-oxotetrahydro saccharin as a pale yellow foam.

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The tetrahydrosaccharin (0.59 g, 1.7 mmol) was dissolved in toluene (50 ml), dimethylamine hydrochloride (1.5 g, 18.0 mmol) and 4 A sieves (2.0 g) were added. The resulting mixture was refluxed with azeotropic removal of water for 96 hr. It was necessary to add additional dimethylamine hydrochloride (0.8 g, 10.0 mmol) and 4 A sieves every 12 hr during this 96 hr period at the end of which time, the reaction mixture was cooled to room temperature and filtered. The filter cake was washed with diethyl ether (100 ml) and the combined filtrates were concentrated in vacuo to give 0.63 g (99% of 2-benzyl-4-isopropyl-6-dimethylamino-(4,5)dihydrosaccharin as a pale yellow solid.

To a solution of the dihydrosaccharin (0.63 g, 1.7 mmol) in refluxing chloroform (50 ml) was added activated manganese dioxide (4.3 g, 49.5 mmol) in portions over a period of 4 hr. After the addition of the last portion of manganese dioxide, the reaction was refluxed for an additional hr, cooled to room temperature and filtered through a pad of super cel, eluting with ethyl acetate. The combined eluents were concentrated in vacuo and the residue purified by flash chromatography on silica gel (5:4:1, hexanes:MDC:ether) to give 0.32 g (50%) of 2-benzyl-4-isopropyl-6-dimethyl-aminosaccharin as a colorless solid.

The 2-benzylsaccharin (0.32 g, 0.9 mmol) in methanol (20 ml) was treated with ammonium formate (0.24 g, 3.8 mmol) and 10% Pd on Carbon (0.25 g) and refluxed for 1 hr, cooled to room temperature and filtered through a pad of super cel, eluting with methanol (100 ml). The combined eluents were concentrated in vacuo. The residue was dissolved in MDC (10 ml), glacial acetic acid (0.25 ml) was added, stirred for 5 min. and evaporated to dryness in vacuo to give 0.25 g (100%) of 4-isopropyl-6-dimethylamino-saccharin as a colorless foam.

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Following a procedure similar to that described in Preparation 1, a mixture of 4-isopropyl-6-dimethylaminosaccharin [I] (0.27 g, 1.0 mmol), chloromethyl phenylsulfide (0.32 g, 2.0 mmol) and TBAB (0.1 g, 0.2 mmol) in toluene was converted to 0.22 g (56%) of 2-phenylthiomethyl-4-iso-propyl-6-dimethylaminosaccharin which was treated with sulfuryl chloride (1.86 ml 0.31 M solution, 0.6 mmol) to give 0.15 g of a yellow gum that contained 25% (by NMR) of the desired product.

28A. Preparation of 2-chloromethyl-6,7-dimethoxy-4-isopropylsaccharin [IV; R^4=iPr; R^5=6-MeO,7-MeO; X=Cl]

31 g 4-isopropyl-1,2-dimethoxybenzene was treated with N-bromosuccinimide followed by butyllithium and diethyl carbamyl chloride as in preparation 6B to yield 15.2 g 2-isopropyl-4,5-di-methoxy-N,N-diethyl-benzamide [V] as a viscous oil. The benzamide was treated according to preparation 18B with butyllithium and sulfur dioxide followed by sulfuryl chloride then ammonia to provide 4.5 g of the sulfonamide, mp 181-182° from ether. This was cyclized in acetic acid as in preparation 18B to obtain 2.86 g of 4-isopropyl-6,7-dimethoxysaccharin, mp 210-212° from ethyl acetate-hexane.

To a solution of 0.5 g 4-isopropyl-6,7-dimethoxysaccharin in 3 ml DMF was added 0.5 ml diisopropylethylamine at room temperature. After 15 min, 0.35 g chloromethyl phenyl sulfide was added and the mixture heated at 80° for 16 hrs. The reaction mixture was poured into EtOAc and washed with aqueous Na_2CO_3 solution, aqueous 2N HCl solution, saturated aqueous NaCl solution. The organic layer was dried over Na_2SO_4 and the solvents removed. Chromatography with MDC gave 0.35 g of desired product, which was used immediately. Treatment of the 0.35 g sample of phenylthiomethyl saccharin in 3 ml MDC with 0.1 ml sulfuryl chloride for 30 min at 20° followed by removal of solvents and

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trituration with hexane gave 0.3 g of the desired product.

28B. Preparation of 2-chloromethyl-4-isopropyl-6,7-methylenedioxysaccharin

[IV; R^4=iPr; R^5=6,7-OCH_2O; X=Cl]

To a solution of 5.7 g methyl piperonylate in 20 ml dry ether was added 30 ml 3.0 methyl magnesium bromide in ether at 0° over 20 min. The mixture was stirred for 20 hrs then diluted with 200 ml ether and washed with water. The organic layer was dried with Na_2SO_4 and the solvents removed to yield 5.6 g crude 3,4-dimethoxy-(1'-hydroxy-1'-methylethyl)benzene. This material was immediately treated in 50 ml acetic acid with 1 g 10% Pd/C under 50 psi hydrogen for 20 hrs. Filtration to remove catalyst and removal of solvent yielded 4.5 g of 5-isopropyl-1,3-benzodioxole. The isopropyldioxole was brominated, amidated, sulfonated and cyclized as in 28A to yield 700 mg of 4-isopropyl-6,7-methylenedioxysaccharin, [II] mp 226-228° from ethyl acetate/hexane. 500mg of the saccharin was chloromethylated as in 28A to provide 300 mg of the desired product, mp 174-176°.

Other 4-R^4-R^5-saccharins of formula II useful as intermediates for the preparation of the compounds of formula I can be prepared as follows.

Reaction of 2-trifluoromethylbenzoic acid with thionyl chloride affords 2-trifluoromethylbenzoyl chloride, which, on reaction with diethylamine, affords 2-trifluoromethyl-N,N-diethylbenzamide. Following a procedure similar to that described in Preparation 5, reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 2-trifluoromethyl-6-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-trifluoromethylsaccharin.

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Similarly, reaction of 2-trichloromethylbenzoic acid with thionyl chloride affords 2-trichloromethylbenzoyl chloride, which, on reaction with diethylamine, affords 2-trichloromethyl-N,N-diethylbenzamide. Following a procedure similar to that described in Preparation 5, reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 2-trichloromethyl-6-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-trichloromethylsaccharin.

Reaction of 4-cyclohexylbenzoic acid with thionylchloride affords 4-cyclohexylbenzoyl chloride, which, on reaction with diethylamine, affords 4-cyclohexyl-N,N-diethylbenzamide. Following a procedure similar to that described in Preparation 5, reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 4-cyclohexyl-2-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 6-cyclohexyl saccharin.

Reaction of a 2-benzyl-6-aminosaccharin with methanesulfonyl chloride, trifluoromethylsulfonyl chloride or trichloromethylsulfonyl chloride in MDC in the presence of pyridine followed by transfer hydrogenolysis of the 2-benzyl protecting group, affords, respectively, 6-methylsulfonylaminosaccharin, 6-trifluoromethylsulfonylaminosaccharin or 6-trichloromethylsulfonylaminosaccharin.

Diazotization of 6-aminosaccharin with nitrous acid in an acid medium and decomposition of the resulting diazonium salt in the presence of cupric cyanide or cupric chloride and sulfur dioxide, or cupric chloride and an alkali metal salt of methyl mercaptan or trifluoromethyl mercaptan affords, respectively,

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6-cyanosaccharin, 6-chlorosulfonylsaccharin, 6-methylthiosaccharin or 6-trifluoromethylthiosaccharin. Reaction of the 6-chlorosulfonylsaccharin in situ with ammonia or methanesulfonylamide affords, respectively, 6-aminosulfonylsaccharin and 6-methanesulfonylaminosulfonylsaccharin. Oxidation of 6-methylthiosaccharin and 6-trifluoromethylthiosaccharin with two molar equivalents of 3-chloroperbenzoic acid affords 6-methylsulfonylsaccharin and 6-trifluoromethylsulfonylsaccharin, respectively.

Hydrolysis of 6-cyanosaccharin by heating with aqueous sodium hydroxide affords saccharin-6-carboxylic acid. Reaction of 6-cyanosaccharin by heating with a catalytic amount of sulfuric acid in ethanol solution affords ethyl saccharin-6-carboxylate, which, on reduction with lithium borohydride, affords 6-hydroxymethylsaccharin. Alternatively, and preferably, the latter compound can be prepared as follows: N-benzylation of 6-cyanosaccharin affords 2-benzyl-6-cyanosaccharin. The latter on alkaline hydrolysis affords 2-benzylsaccharin-6-carboxylic acid which on conversion to 2-benzylsaccharin-6-carboxylic acid chloride by reaction with thionyl chloride, followed by exhaustive hydrogenation over palladium on carbon affords 6-hydroxymethylsaccharin. Oxidation of the latter with pyridine:chromium trioxide (2:1) complex (Collins reagent) in MDC affords 6-formylsaccharin, which, on reductive amination with ammonia and sodium cyanoborohydride, affords 6-aminomethylsaccharin.

Reaction of 4-trifluoromethylbenzoic acid with thionyl chloride affords 4-trifluoromethylbenzoyl chloride, which, on reaction with diethylamine, affords 4-trifluoromethyl-N,N-diethylbenzamide. Following a procedure similar to that described in Preparation 5, reaction of the latter with s-butyl lithium and reaction

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of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 4-trifluoromethyl-2-aminosulfonyl-N,N-diethylbenzamide, which on heating in glacial acetic acid, affords 6-trifluoromethylsaccharin.

Reaction of 4-trichloromethylbenzoic acid with thionyl chloride affords 4-trichloromethylbenzoyl chloride, which, on reaction with diethylamine, affords 4-trichloromethyl-N,N-diethylbenzamide. Following a procedure similar to that described in Preparation 5, reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 4-trichloromethyl-2-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 6-trichloromethylsaccharin.

Reaction of 2-ethenylbenzoic acid with thionyl chloride affords 2-ethenylbenzoyl chloride, which on reaction with diethylamine, affords 2-ethenyl-N,N-diethylbenzamide. Reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 2-ethenyl-6-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-ethenylsaccharin.

Reaction of 2-ethenyl-6-aminosulfonyl-N,N-diethylbenzamide with bromine affords 2-(1,2-dibromoethyl)-6-aminosulfonyl-N,N-diethylbenzamide which, on reaction with sodium amide in ammonia affords 2-ethynyl-6-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-ethynylsaccharin.

Reaction of ethyl 2-aminobenzoate with two molar equivalents of benzyl chloride in acetone in the presence of potassium carbonate affords ethyl

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2-(N,N-dibenzylamino)benzoate which, on saponification in aqueous ethanolic potassium hydroxide and isolation of the product from a neutral medium, affords 2-(N,N-dibenzylamino)benzoic acid.

Reaction of the latter with thionyl chloride affords 2-(N,N-dibenzylamino)benzoyl chloride, which, on reaction with diethylamine, affords 2-(N,N-dibenzylamino)-N,N-diethylbenzamide. Reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 2-(N,N-dibenzyl)-6-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-(N,N-dibenzylamino)-saccharin which, on catalytic debenzylation with hydrogen over palladium-on-charcoal, affords 4-amino-saccharin. Reductive alkylation of the latter with one molar equivalent of formaldehyde in formic acid affords 4-methylaminosaccharin.

Diazotization of 4-aminosaccharin with nitrous acid in an acid medium and decomposition of the resulting diazonium salt in the presence of cupric cyanide affords 4-cyanosaccharin.

Reaction of 4-isopropyl-6-hydroxysaccharin (Preparation 19) with N,N-diethylthiocarbamyl chloride in DMF using the procedure described above in Preparation 12 affords 4-isopropyl-6-(N,N-diethylthiocarbamyloxy)saccharin which, on heating, rearranges to 4-isopropyl-6-(N,N-diethylcarbamylthio)saccharin. The latter, on hydrolysis with alkali, affords 4-isopropyl-6-mercaptosaccharin which, after benzylation, reaction with methyl iodide, and transfer hydrogenolysis affords 4-isopropyl-6-methylthiosaccharin. Alternatively, and preferably, the latter can be prepared as follows. Selective N-benzylation of the cesium salt of 4-isopropyl-6-hydroxysaccharin (Preparation 19) with benzyl bromide and reaction of the 2-benzyl-4-isopropyl-

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6-hydroxysaccharin with N,N-diethylthiocarbamyl chloride in DMF using the procedure described above in Preparation 12 affords 2-benzyl-4-isopropyl-6-(N,N-diethylthiocarbamyloxy)saccharin which, on heating, rearranges to 2-benzyl-4-isopropyl-6-(N,N-diethylcarbamylthio)saccharin. The latter, on hydrolysis with alkali, affords 2-benzyl-4-isopropyl-6-mercaptosaccharin which on reaction with methyl iodide, and transfer hydrogenolysis affords 4-isopropyl-6-methylthiosaccharin. Oxidation of the latter with one or two molar equivalents of 3-chloroperbenzoic acid affords 4-isopropyl-6-methylsulfinylsaccharin and 4-isopropyl-6-methylsulfonylsaccharin.

Reaction of 2-isopropyl-4-fluorobenzoic acid with thionyl chloride affords 2-isopropyl-4-fluorobenzoyl chloride, which, on reaction with diethylamine, affords 2-isopropyl-4-fluoro-N,N-diethylbenzamide. Reaction of the latter with s-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 2-isopropyl-4-fluoro-6-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-isopropyl-6-fluorosaccharin.

Reaction of the latter with thiophenol, 4-methylphenylthiophenol, 4-methoxyphenylthiophenol, 4-chlorophenylthiophenol, 1-mercapto-4-methylnaphthalene or 1-mercaptonaphthalene by heating the reactants in DMF affords, respectively, 4-isopropyl-6-phenylthiosaccharin, 4-isopropyl-6-(4-methylphenylthio)saccharin, 4-isopropyl-6-(4-methoxyphenylthio)saccharin, 4-isopropyl-6-(4-chlorophenylthio)saccharin, 4-isopropyl-6-(4-methyl-1-naphthylthio)saccharin and 4-isopropyl-6-(1-naphthylthio)saccharin. Oxidation of the latter with one or two molar equivalents of 3-chloroperbenzoic acid affords 4-isopropyl-6-phenylsulfinylsaccharin, 4-isopropyl-6-phenylsulfonylsaccharin, 4-isopropyl-

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6-(4-methylphenylsulfinyl)saccharin, 4-isopropyl-6-(4-methylphenylsulfonyl)saccharin, 4-isopropyl-6-(4-methoxyphenylsulfinyl)saccharin, 4-isopropyl-6-(4-methoxyphenylsulfonyl)saccharin, 4-isopropyl-6-(4-chlorophenylsulfinyl)saccharin, 4-isopropyl-6-(4-chlorophenylsulfonyl)saccharin, 4-isopropyl-6-(4-methyl-1-naphthylsulfinyl)saccharin, 4-isopropyl-6-(4-methyl-1-naphthylsulfonyl)saccharin, 4-isopropyl-6-(1-naphthylsulfinyl)saccharin and 4-isopropyl-6-(1-naphthylsulfonyl)saccharin.

Reaction of 4-isopropyl-6-hydroxysaccharin (Preparation 19) with one molar equivalent of acetic anhydride, benzoyl chloride or 1-naphthyl carboxylic acid chloride affords, respectively, 4-isopropyl-6-acetoxysaccharin, 4-isopropyl-6-benzoyloxysaccharin and 4-isopropyl-6-(1-naphthylcarbonyloxy)saccharin. Alternatively, and preferably, these three compounds can be prepared by reaction of 2-benzyl-4-isopropyl-6-hydroxysaccharin with one molar equivalent of acetic anhydride, benzoyl chloride or 1-naphthyl carboxylic acid chloride followed in each case by transfer hydrogenolysis.

Heating 4-isopropyl-6-fluorosaccharin in DMF with azetidine, pyrrolidine, piperidine, morpholine, 1-benzylpiperazine, 1-methylpiperazine, imidazole, t-butyl alpha-amino-acetate or ammonia affords, respectively, 4-isopropyl-6-(1-azetidinyl)saccharin, 4-isopropyl-6-(1-pyrrolidinyl)saccharin, 4-isopropyl-6-(1-piperidinyl)saccharin, 4-isopropyl-6-(4-morpholinyl)saccharin, 4-isopropyl-6-(4-benzyl-1-piperazinyl)saccharin, 4-isopropyl-6-(4-methyl-1-piperazinyl)saccharin, 4-isopropyl-6-(1-1H-imidazolyl)saccharin, 4-isopropyl-6-(carbo-t-butoxymethylamino)saccharin and 4-isopropyl-6-amino-saccharin.

Catalytic debenzylation of 4-isopropyl-

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6-(4-benzyl-1-piperazinyl)saccharin with hydrogen over palladium on charcoal affords 4-isopropyl-6-(1-piperazinyl)saccharin.

Hydrolysis of 4-isopropyl-6-(carbo-t-butoxy-carbonylmethylamino)saccharin with dilute hydrochloric acid and isolation of the product from a neutral medium affords 4-isopropyl-6-carboxymethylaminosaccharin.

Reaction of 4-isopropyl-6-aminosaccharin with one molar equivalent of acetyl chloride affords 4-isopropyl-6-acetylaminosaccharin.

Saponification of 4-carbomethoxysaccharin (Preparation 9D) to the corresponding saccharin-4-carboxylic acid by alkaline hydrolysis, conversion of the acid to the corresponding acid chloride by reaction of the acid with thionyl chloride and reaction of the acid chloride with ammonia affords saccharin-4-carboxamide.

Conversion of saccharin-6-carboxylic acid to the corresponding acid chloride by reaction of the acid with thionyl chloride and reaction of the acid chloride with ammonia affords saccharin-6-carboxamide.

Reaction of each of the 4-R^4-R^5-saccharins so-prepared with paraformaldehyde and chlorotrimethylsilane in the presence of stannic chloride in ethylene dichloride affords the 4-R^4-R^5-2-chloromethylsaccharins of formula IV listed in TABLE B where, in each instance, X is Cl.

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TABLE B

Preparation	R^4	R^5
19A	CF_3	H
19B	CCl_3	H
19C	H	6-cyclohexyl
19D	H	6-CH_3SO_2NH
19E	H	6-CF_3SO_2NH
19F	H	6-CCl_3SO_2NH
19G	H	6-CN
19H	H	6-NH_2SO_2
19I	H	6-$CH_3SO_2NHSO_2$
19J	H	6-CH_3SO_2
19K	H	6-CF_3SO_2
19L	H	6-HOOC
19M	H	6-$HOCH_2$
19N	H	6-OHC
19-O	H	6-NH_2CH_2
19P	H	6-CF_3
19Q	H	6-CCl_3
19R	$CH=CH_2$	H
19S	C≡CH	H
19T	NH_2	H
19U	CH_3NH	H
19V	$(CH_3)_2N$	H
19W	$CH(CH_3)_2$	6-CH_3S
19X	$CH(CH_3)_2$	6-CH_3SO
19Y	$CH(CH_3)_2$	6-CH_3SO_2
19Z	$CH(CH_3)_2$	6-F
19AA	$CH(CH_3)_2$	6-C_6H_5S
19AB	$CH(CH_3)_2$	6-(4-$CH_3C_6H_4S$)
19AC	$CH(CH_3)_2$	6-(4-$CH_3OC_6H_4S$)
19AD	$CH(CH_3)_2$	6-(4-ClC_6H_4S)
19AE	$CH(CH_3)_2$	6-(4-CH_3-1-naphthyl-S)
19AF	$CH(CH_3)_2$	6-(1-naphthyl-S)
19AG	$CH(CH_3)_2$	6-C_6H_5SO
19AH	$CH(CH_3)_2$	6-$C_6H_5SO_2$

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TABLE B cont'd.

Preparation	R^4	R^5
19AI	$CH(CH_3)_2$	6-(4-$CH_3C_6H_4SO$)
19AJ	$CH(CH_3)_2$	6-(4-$CH_3C_6H_4SO_2$)
19AK	$CH(CH_3)_2$	6-(4-$CH_3OC_6H_4SO$)
19AL	$CH(CH_3)_2$	6-(4-$CH_3OC_6H_4SO_2$)
19AM	$CH(CH_3)_2$	6-(4-ClC_6H_4SO)
19AN	$CH(CH_3)_2$	6-(4-$ClC_6H_4SO_2$)
19AO	$CH(CH_3)_2$	6-(4-CH_3-1-naphthyl-SO)
19AP	$CH(CH_3)_2$	6-(4-CH_3-1-naphthyl-SO_2)
19AQ	$CH(CH_3)_2$	6-(1-naphthyl-SO)
19AR	$CH(CH_3)_2$	6-(1-naphthyl-SO_2)
19AS	$CH(CH_3)_2$	6-CH_3COO
19AT	$CH(CH_3)_2$	6-C_6H_5COO
19AU	$CH(CH_3)_2$	6-(1-naphthyl-COO)
19AV	$CH(CH_3)_2$	6-(1-azetidinyl)
19AW	$CH(CH_3)_2$	6-(1-pyrrolidinyl)
19AX	$CH(CH_3)_2$	6-(1-piperidinyl)
19AY	$CH(CH_3)_2$	6-(4-morpholinyl)
19AZ	$CH(CH_3)_2$	6-(4-benzyl-1-piperazinyl)
19BA	$CH(CH_3)_2$	6-(4-methyl-1-piperazinyl)
19BB	$CH(CH_3)_2$	6-(1-1H-imidazolyl)
19BC	$CH(CH_3)_2$	6-($NHCH_2COOC_4H_9$-t)
19BD	$CH(CH_3)_2$	6-NH_2
19BE	$CH(CH_3)_2$	6-(1-piperazinyl)
19BF	$CH(CH_3)_2$	6-($NHCH_2COOH$)
19BG	$CH(CH_3)_2$	6-(CH_3CONH)
19BH	$CONH_2$	H
19BK	CN	H
19BL	H	$CONH_2$

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19BI. Preparation of 2-chloromethyl-4-spirocyclopropyl-4,5,6,7-tetrahydrosaccharin

Reaction of isothiazole-5-carboxaldehyde with lithium 3-(triphenylphosphoranylidene)propanoate under standard Wittig conditions provides 4-(5-isothiazolyl)-3-butenoic acid which is reduced and cyclized with aluminum chloride to provide 4-oxo-4,5,6,7-tetrahydrobenzisothiazole. The 4-oxo compound is reacted with methylenetriphenyl phosphorane under standard Wittig conditions and a methylene is inserted into the resulting 4-methylene compound via a Simmons Smith reaction to provide 6,7-dihydrospiro[benzisothiazol-4(5H),1'-cyclopropane] which is oxidized with hydrogen peroxide in acetic acid to give 6,7-dihydrospiro[3-oxo-benzisothiazol-4(5H),1'-cyclopropane 1,1-dioxide (4-spircyclopropyl tetrahydrosaccharin). This is chloromethylated according to the procedure of Preparation 1A to give the desired product.

19BJ. Preparation of 2-chloromethyl-4-isopropyl-6-methoxy-4,5,6,7-tetrahydrosaccharin

2-Benzyl-4-isopropyl-6-oxotetrahydrosaccharin of preparation 23 is reduced with sodium borohydride and methylated with methyl iodide in the presence of sodium hydride to provide 2-benzyl-4-isopropyl-6-methoxytetrahydrosaccharin. This is debenzylated and chloromethylated as in Preparation 23 to provide the desired product.

20A. Preparation of 2,6-difluoro-3-(4-methyl-1-piperazinyl)sulfonylbenzoic acid

A mixture of 10.0 g (0.063 mol) 2,6-difluorobenzoic acid and 66.0 g (0.57 mol) chlorosulfonic acid was heated at 155-160°C and then poured carefully into 100 ml ice water. The solids which separated were collected by filtration, air dried and recrystallized from chloroform to give 7.0 g of 3-chlorosulfonyl-

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2,6-difluorobenzoic acid, 0.64 g (0.0025 mol) of which was dissolved in MDC and treated at -10°C with a solution of 0.25 g (0.0025 mol) 1-methylpiperazine and 0.33 g (0.0026 mol) diisopropylethylamine. The product which separated was collected by filtration, washed with MDC and dried to give 0.4 g (50%) of the desired product.

20B-20G. Preparation of 3-aminosulfonyl-2,6-dichlorobenzoic acids

Following a procedure similar to that described in Preparation 20A above, 3-chlorosulfonyl-2,6-dichlorobenzoic acid, m.p. 172-175°C (from chloroform) was prepared in 56% yield by heating a mixture of 2,6-dichlorobenzoic acid with chlorosulfonic acid at 150-160°C.

Reaction of the latter with an appropriate amine (N=B) afforded the 3-aminosulfonyl-2,6-dichlorobenzoic acids listed in TABLE C below. In each instance products were not further purified but were used as such in the next step.

TABLE C

Preparation	N=B	Yield
20B	4-morpholinyl	86
20C	$NHCH_2COO-C_4H_9-(t)$	36
20D	$4-CH_3-1$-piperazinyl	40
20E	$4-C_6H_5CH_2-1$-piperazinyl	59
20F	$N(CH_3)CH_2CH_2N(CH_3)_2$	82
20G	$NHCH_2COOBzl$	50

21A. Preparation of 2,6-dichloro-3-[2-(4-morpholinyl)-ethoxy]benzoic acid

To a mixture of 1.0 g (0.003 mol) benzyl 2,6-dichloro-3-hydroxybenzoate and 0.18 g 60% dispersion of sodium hydride in mineral oil in 30 ml DMF was added

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a solution of 0.008 mol 4-(2-chloroethyl)morpholine in 20 ml t-butyl methyl ether and the mixture heated at 70°C for three hours. The reaction mixture was then taken to dryness and the residue taken up in ethyl acetate and the organic solution washed with water and brine, then dried and concentrated in vacuo to dryness to give 1.25 g (83%) of benzyl 2,6-dichloro-3-[2-(4-morpholinyl)ethoxy]benzoate which was dissolved in 1:1 ethyl acetate:methanol (50 ml) and reduced with hydrogen over 0.25 g 10% palladium-on-charcoal. When reduction was complete, the catalyst was removed by filtration, washed with DMF and the combined filtrates taken to dryness in vacuo to give 0.75 g (75%) of the desired product.

21B. Preparation of 2,6-dichloro-3-[2-(dimethylamino)-ethoxy]benzoic acid

Following a procedure similar to that described in Preparation 21A, 1.0 g (0.003 mol) benzyl 2,6-dichloro-3-hydroxybenzoate was reacted with 0.092 mol N-(2-chloroethyl)-N,N-dimethylamine in 30 ml DMF and 20 ml t-butyl methyl ether in the presence of 0.18 g 60% mineral oil dispersion of sodium hydride to give a quantitative yield of benzyl 2,6-dichloro-3-[2-(dimethylamino)ethoxy]benzoate which was reduced catalytically in a 5:2 solution of ethyl acetate:-methanol over 0.2 g 10% palladium-on-charcoal. There was thus obtained 0.2 g (22%) of the desired product.

21C. Preparation of 2,6-dichloro-4[2-(4-morpholinyl)-ethoxy]benzoic acid.

To a solution of methyl 2,6-dichloro-4-methoxybenzoate (J. Org. Chem. 50, 408 1985) (5.5 g, 0.023 mol) in methanol (50 ml) was added 5N sodium hydroxide (20 ml). The resulting mixture was heated at relfux for 20 hr, cooled to room temperature, concentrated in vacuo and acidified to pH 1 with 2N HCl. The separated solids were collected by filtration to

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give 5.2 g (100%) of 2,6-dichloro-4-methoxybenzoic acid, which was treated with 60 ml 1M solution of boron tribromide (0.06 mol) in dichloroethane (100 ml) at reflux for 2 hr. The resulting mixture was cooled to room temperature and poured onto water/methanol (50 ml 9:1 mixture). After stirring for 10 minutes, the mixture was extracted with ether (400 ml) and the organic phase washed with water, brine and dried. Removal of the solvent in vacuo gave 4.0 g (80%) of 2,6-dichloro-4-hydroxybenzoic acid.

The latter (1.05 g, 0.005 mol) was dissolved in 95% ethanol (25 ml) and treated with benzyl chloride (0.71 g, 0.006 mol) and 1N NaOH (5 ml). After refluxing under nitrogen for 2 hr, the reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was acidified with 2N HCl and extracted with ether. The organic phase was washed with saturated $NaHCO_3$, water and 10% NaOH. After discarding the organic phase, the NaOH washings were acidified with 2N HCl and re-extracted with ether (2 x 50 ml). The ether extract was then dried and concentrated in vacuo to give 0.63 g (42%) of benzyl-2,6-dichloro-4-hydroxybenzoate.

Following a procedure similar to that described in Preparation 21A, 630 mg benzyl 2,6-dichloro-4-hydroxybenzoate was converted to 350 mg of the desired product.

24A. Preparation of 2,6-dichloro-3-[2-(dimethylamino)-ethoxy]benzoic acid

A solution of 1.9 g (0.01 mol) 2,6-dichloro-3-hydroxybenzaldehyde in 10 ml dry DMF was flushed with nitrogen and 0.3 g 97% sodium hydride was added with magnetic stirring. Hydrogen was evolved giving a clear red-brown solution. To this was added a solution of 2-dimethylaminoethylchloride (from 2.0 g of the hydrochloride) in 6 ml t-butylmethyl ether. The solution was

heated to reflux for 1/2 hr. Sodium chloride precipitated. The condenser was removed and heating was continued for 1/2 hr. The reaction mixture was concentrated to dryness, taken up in dilute HCl and extracted with methylene chloride. The aqueous layer was basified with 10% Na_2CO_3 solution, extracted 3X with CH_2Cl_2 and the extracts evaporated to a brown oil which was distilled in a Kugelrohr, bp 155-160°/0.12 mm. The yellow distillate crystallized and was converted to the hydrochloride with ethereal HCl. Recrystallization from CH_3CN gave 661 mg of 2,6-dichloro-3-[2-dimethylamino)-ethoxy]benzaldehyde hydrochloride, mp 177-178°C.

Freshly prepared silver oxide (from 1.7 g $AgNO_3$) was suspended in 1.0 ml 10% sodium hydroxide solution which was then heated to 55°. The aldehyde (2.62 g, 0.01mm) was added with magnetic stirring. The exothermic reaction raised the temperature to 65° and silver precipitated. Heating was continued at 60° for 1/4 hr. The reaction was filtered and the filtrate extracted 2X with CH_2Cl_2. Evaporation of the CH_2Cl_2 gave 0.804 g of starting aldehyde. The aqueous phase was acidified with 3N HCl and evaporated in vacuo to a white solid which was recrystallized from 10 ml water. There was obtained 1.065 g (34%) of the desired product. mp 234-236°C.

24B-24D. Preparations of aldehydes and acids

Following a procedure similar to that described in Preparation 24A above, the aldehydes and acids shown in Table D were prepared:

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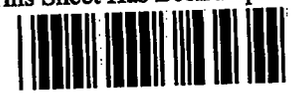
TABLE_D

preparation	O-alkylene-N=B	Aldehyde bp	yield	Acid HCl Salt mp	yield
24B	2-(1-pyrrolidinyl)-ethoxy	130-140/0.1 mm	41	253-255	10
24C	2-(1-piperdinyl)ethoxy	160-180/0.1 mm	54	241-242	24
24D	2-(diethylamino)ethoxy	not distilled	--	220-222	15

25. Preparation of 2,6-dichloro-3-benzyloxybenzoic acid

To a solution of chlorine (15.7 g, 0.22 mol) in glacial acetic acid (250 ml) at 0°C was added methyl 3-hydroxybenzoate (15.2g, 0.1 mol). The resulting solution was warmed to room temperature and stirred for 1 hr and evaporated to dryness in vacuo to give 21.4 g of a yellow oil which was found to contain 75% methyl 2,6-dichloro-3-hydroxybenzoate by NMR. The oil (21.4 g) was dissolved in acetone (600 ml), benzyl bromide (19.9 g, 0.12 mol) and potassium carbonate (22.7 g, 0.16 mol) were added and refluxed under nitrogen for 16 hr. The reaction mixture was cooled to room temperature and the solids filtered off. The filtrate was concentrated in vacuo and the residue taken up in 10% ethyl acetate in hexanes (100 ml) and chilled in an ice bath. The solids that emerged were collected by filtration and air dried to give 14.3 g (47%) of methyl 2,6-dichloro-3-benzyloxybenzoate.

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A solution of methyl 2,6-dichloro-3-benzyloxybenzoate (2.1 g, 6.7 mmol) and 10% aqueous NaOH (25 ml) in methanol (25 ml) was refluxed under nitrogen for 24 hr and cooled to room temperature. The resulting mixture was concentrated to one-half the volume in vacuo and acidified to pH 1 with 2N HCl. the solids that precipitated were collected by filtration, washed with water, hexanes and air dried to give 2.0 g (100%) of the desired product as a white solid.

26. Preparation of 3-acetylamino-2,6-dimethoxybenzoic acid

A solution of 5 g 2,6-dimethoxy-3-nitrobenzoic acid in THF was hydrogenated in the presence of 10% Pd on C and the resulting amine was acetylated in situ with acetic anhydride and pyridine to provide 0.9 g of the desired product.

27. Preparation of chloromethyl 2,6-dichlorobenzoate

To a suspension of 3.6 g (0.12 mol) paraformaldehyde in 50 ml 1,2-dichloroethane and 30 ml (26 g, 0.24 mol) trimethylsilyl chloride under nitrogen was added 0.2 ml stannic chloride and the resulting solution was stirred on a steam bath. After 30 min, 9.55 g (0.05 mol) 2,6-dichlorobenzoic acid was added and the reaction heated for an additional 20 hours. Volatiles were removed, the residue dissolved in MDC and washed with $NaHCO_3$, dried and stripped to an oil which was triturated in hexane and filtered to obtain 8.5 g of the desired product.

29. Preparation of 4-(2-hydroxymethyl)-1-carbobenzyloxypiperidine.

A mixture of 4-piperidinethanol (2.9 g, 100 mol), THF (350 ml) and 4N NaOH (200 ml) was cooled to 0°C and a solution of carbobenzyloxy chloride (26.0 ml, 180 mmol) in THF (50 ml) was added at such a rate as to keep the internal reaction temperature below 5°C. The reaction mixture was stirred at 0°C for

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2 hours, and then partitioned between water (250 ml) and ether (250 ml). The layers were separated, and the aqueous layer was extracted with ether (2 x 100 ml). The ether extracts were combined, washed with brine, dried over $MgSO_4$, filtered through florisil and concentrated in vacuo. The residue was purified by High Pressure Liquid Chromatography (HPLC) eluting with ethyl acetate to afford 24.8 g (94.3%) of the desired product.

30. Preparation of N,N-dibenzyl-2-bromoacetamide

To a mixture of dibenzylamine (2.0 g, 10.14 mmol) and N,N-dimethylaniline (1.23 g, 10.14 mmol) at 0°C under N_2 was added dropwise bromoacetylbromide (2.05 g, 10.14 mmol). The reaction mixture was stirred for two hours, and the mixture was concentrated in vacuo. The residue was taken up in ethyl acetate/-5% citric acid and washed with additional citric acid, then 50% saturated $NaHCO_3$ (2X) and finally brine. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo to afford a brown oil. The oil was extracted with ethyl acetate, washed with 1N HCl and the organic solvent was removed in vacuo to afford 2.344 g (72.6%) of the desired product.

31. Preparation of 5-dimethylaminomethyl-2-hydroxy-methylfuran

To a solution of furfuryl alcohol (19.6 g, 0.199 mol) in acetic acid (125 ml) at 0-10°C was added dropwise a solution of bis-dimethylaminomethane (30.62 g, 0.299 mol) in acetic acid (60 ml) over approx. 1 hour. The reaction mixture was warmed to room temperature and stirred for 18-19 hours. The excess acetic acid was removed in vacuo and the residue thus obtained was treated with 30% NaOH. The mixture was extracted with ethyl acetate (3X) and the organic layers were combined, dried and concentrated in vacuo. The residue was distilled at 130-135°C and 3-3.5 mm Hg to afford 26.3 g (85%) of the desired product.

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32. Preparation of 2-chloromethyl-4-ethoxy-6-hydroxy-saccharin.[IV; R^4=EtO; R^5=6-OH; X=Cl]

(a) To a suspension of 4-bromoresorcinol (40.0 g, 211.6 mmol), and K_2CO_3 (188.01 g, 1360.32 mmol) in acetone was added tosyl chloride (40.34 g, 211.6 mmol). The mixture was stirred at reflux under N_2 for 20 hours and then ethyl iodide (95.21 g, 566.8 mmol) was added in one portion to the warm flask and the mixture was stirred for 2 hours. The reaction mixture was cooled, diluted with ether and filtered and the filtrate was concentrated in vacuo to afford 77.91 g (99%) of 1-bromo-2-ethoxy-4-p-toluenesulfonyloxybenzene as a yellow solid.

(b) To a mixture of 1-bromo-2-ethoxy-4-p-toluene-sulfonyloxybenzene (77.91 g, 209.86 mmol) in ethanol (500 ml) and water (500 ml) was added KOH (60 g). The mixture was refluxed for 2 hours and was then cooled and neutralized with acetic acid. The mixture was extracted with ether (3X), the ether extracts were combined and extracted with 3% KOH. The basic aqueous phase was acidified to a pH of 1 with 6N HCl and the acidic solution was extracted with ether (3X). The combined ether extracts were dried over $MgSO_4$ and the solvent was removed in vacuo to afford 41.42 g (90.9%) of 1-bromo-2-ethoxy-4-hydroxybenzene as an amber oil.

Alternatively, the latter compound was prepared as described hereinbelow. A mixture of 4-bromoresorcinol (47.230 g, 249.88 mmol), ethyl iodide (33.58 g, 199.90 mol) and potassium carbonate (103.61 g, 749.64 mmol) in acetone was stirred at room temperature under N_2 for 24 hours. The reaction mixture was diluted with ether (600 ml), filtered and the filtrate was concentrated in vacuo to a brown oil. The oil was taken up in ether, washed with water (250 ml, 2X) and the ether layer was extracted with 5% NaOH. The basic extract was acidified with 6N HCl to a pH of 1 and the

mixture was extracted with ether (4X). The ether extracts were combined, washed with water, and dried over Na_2SO_4 and concentrated in vacuo to a yellow-orange oil. The oil was taken back up in ether and was washed with 10% K_2CO_3 (100 ml, 7X). The ether layer was dried over Na_2SO_4 and concentrated in vacuo to afford 20.75 g (47.8%) of 1-bromo-2-ethoxy-4-hydroxybenzene as a yellow oil.

(c) A mixture of 1-bromo-2-ethoxy-4-hydroxybenzene (36.83 g, 169.68 mmol), tert-butyldimethylsilyl chloride (56.26 g, 373.26 mmol) and imidazole (50.82 g, 746.53 mmol) in DMF (350 ml) was stirred at room temperature under N_2 for 2 1/2 hours. The reaction mixture was diluted with ether and washed with water (5X), and then brine. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo to afford 53.01 g (94.3%) of 1-bromo-2-ethoxy-4-tert-butyldimethylsilyloxybenzene.

(d) A mixture of 1-bromo-2-ethoxy-4-tert-butyl-dimethylsilyloxybenzene (52.29 g, 157.82 mmol) and ether was cooled to 0°C under N_2 and n-BuLi (74.14 ml, 2.15 M hexane, 159.49 mmol) was added dropwise. The mixture was stirred at 0°C for a few hours, the mixture was cooled to -78°C and then diethylcarbamyl chloride (21.40 g, 157.82 mmol) was added. The mixture was stirred for 2 hours, quenched with saturated NH_4Cl and the organic layer was separated. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography on silica eluting with 20% ethyl acetate/hexane to afford 39.25 g (70.7%) of 2-ethoxy-4-t-butyldimethylsilyloxy-N,N-diethylbenzamide as a yellow oil which solidified on standing.

(e) A solution of 2-ethoxy-4-t-butyldimethylsilyloxy-N,N-diethylbenzamide (15.0 g, 42.67 mmol) in THF

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100 ml) was added to a mixture of sec-BuLi (37.0 ml, 1.21 M solution, 44.80 mmol) and TMEDA (4.95 g, 42.67 mmol) in THF (500 ml) at -78°C under N_2. The mixture was then stirred for 2 hours and condensed liquid sulfur dioxide (50 ml) at -78°C was added in one portion. Stirring was continued for 17 hours during which time the reaction temperature rose to 15°C. The reaction solvent was removed in vacuo to afford a yellow solid, which was taken up in water (800 ml) and cooled to 0°C. A mixture of NaOH (5.29 g, 132.28 mmol) in water at 0°C was then added to a cooled solution of hydroxylamine-O-sulfonic acid (14.96 g, 132.28 mmol) in water (100 ml). This mixture was then added in one portion to the above reaction mixture at 0°C. The mixture was stirred for 5 hours, extracted with CH_2Cl_2 (3X) and the combined organic layers were dried over Na_2SO_4. Removal of the solvent in vacuo afforded crude 2-aminosulfonyl-6-ethoxy-4-t-butyldi-methylsilyloxy-N,N-diethylbenzamide, which was used directly in the next step without further purification.

(f) 2-Aminosulfonyl-6-ethoxy-4-t-butyldimethylsilyl-oxy-N,N-diethylbenzamide (17.38 g, 40.35 mmol) was dissolved in THF, the solution was cooled to 0°C and tetrabutylammonium fluoride (48.42 ml, 48.42 mmol, 1 M solution in THF) was added in one portion. The reaction mixture was stirred for 1/2 hour, and then was poured into water (40 ml). The solution was extracted with ethyl acetate (3X) and the combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude oil thus obtained was combined with the crude product obtained from a similar experimental run starting with 1.0 g 2-aminosulfonyl-6-ethoxy-4-t-butyldimethylsilyloxy-N,N-diethylbenzamide and the mixture was purified by column chromatography on silica eluting with 60% ethyl acetate/hexane to afford 7.87 g of 2-aminosulfonyl-4-hydroxy-6-ethoxy-

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N,N-diethylbenzamide.

Alternatively, the latter compound was also prepared by treating 2-aminosulfonyl-6-ethoxy-4-tert-butyldimethylsilyloxy-N,N-diethylbenzamide with two equivalents of potassium fluoride in DMF in the presence of a catalytic amount of 48% HBr at room temperature for 20 minutes; followed by pouring the reaction mixture into ice-cold 1N HCl, extracting the mixture with ethyl acetate (5X), washing the combined organic layers with brine, drying the organic layers over Na_2SO_4 and removing the solvent in vacuo.

(g) 2-Aminosulfonyl-4-hydroxy-6-ethoxy-N,N-diethyl-benzamide (7.87 g, 24.88 mmol) was dissolved in glacial acetic acid (60 ml) and the mixture was refluxed overnight. The mixture was cooled to room temperature, during which time a precipitate formed. The precipitate was removed by filtration and washed with toluene and then CH_2Cl_2. The white solid thus obtained was dried at 60°C under high vacuum for 17 hours to afford 2.40 g (39.7%) 4-ethoxy-6-hydroxysaccharin, m.p. 317°C (dec.).

(h) To 4-ethoxy-6-hydroxysaccharin (2.302 g, 9.46 mmol) in methanol under a nitrogen atmosphere was added cesium carbonate (1.387 g, 4.257 mmol). The mixture was stirred for 1 1/2 hours, the solvent was removed in vacuo, and the residue was dried under high vacuum overnight. The residue was taken up in DMF and chloromethyl phenylsulfide (1.65 g, 10.41 mmol) was added. The mixture was stirred at 75°C under N_2 for 17 hours and then additional chloromethyl phenylsulfide (0.450 g) was added. The mixture was stirred for 2.5 hours, the solvent was removed in vacuo, and the residue was taken up in ethyl acetate. The organic layer was washed with water, then brine, and was then dried over Na_2SO_4. Removal of the solvent in vacuo afforded a yellow oil which was purified by column chromatography on silica eluting with 30% ethyl

acetate/hexane to afford 1.98 g (60.6%) of 2-phenylthiomethyl-4-ethoxy-6-hydroxysaccharin, as a white solid, m.p. 204-205°C.

(i) To a mixture of 2-phenylthiomethyl-4-ethoxy-6-hydroxysaccharin (1.88 g, 5.14 mmol) in CH_2Cl_2 (250 ml) was added sulfuryl chloride (0.833 g, 6.17 mmol) in one portion. The mixture was stirred at room temperature under N_2 for 5 hours, and then the solvent was removed in vacuo. The residue thus obtained was triturated with hexane and the white solid which formed was collected by filtration and dried in high vacuum to afford 1.492 g (99.5%) of 2-chloromethyl-4-ethoxy-6-hydroxysaccharin.

33. Preparation of 2-chloromethyl-4-ethoxy-6-[2-(benzyloxy)ethoxy]saccharin

[IV; R^4=EtO; R^5=2-($C_6H_5CH_2O$)C_2H_4O; X=Cl}

(a) To a solution of 2-phenylthiomethyl-4-ethoxy-6-hydroxysaccharin (1.00 g, 2.74 mmol) in THF at 25°C under N_2 was added triphenylphosphine (0.755 g, 2.88 mmol), followed by 2-benzyloxyethanol (0.438 g, 2.88 mmol) and then diethyl azodicarboxylate (0.524 g, 3.01 mmol). The mixture was stirred at room temperature for 17 hours, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica eluting with 30% ethyl acetate/hexane to afford 1.138 g (85.6%) of 2-phenylthiomethyl-4-ethoxy-6-[2-(benzyloxy)-ethoxy]saccharin as a colorless oil which crystallized on standing.

(b) To a solution of 2-phenylthiomethyl-4-ethoxy-6-[2-(benzyloxy)ethoxy]saccharin (1.017 g, 2.14 mmol) in CH_2Cl_2 under N_2 was added sulfuryl chloride (0.357 g, 2.62 mmol). The mixture was stirred for 3 hours and the solvent was removed in vacuo. The residue was triturated with hexane and the solid which formed was collected to afford 907 mg (99.6%) of the desired product as a gummy yellow solid.

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34. Preparation of 2-chloromethyl-4-propoxy-6-methoxysaccharin [IV; R^4=PrO; R^5=6-MeO; X=Cl]

(a) To a mixture of methyl 2-hydroxy-4-methoxybenzoate (50.00 g, 274.45 mmol) and K_2CO_3 (45.52 g, 329.34 mmol) in DMF (250 ml) at room temperature under N_2 was added propyl iodide (74.64 g, 439.12 mmol). The mixture was heated to 85-90°C for 91 hours, and then the solvent was removed in vacuo. The residue was taken up in CH_2Cl_2, the solution was filtered and the filtrate was washed with saturated sodium bicarbonate, water, and then brine. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo to afford 61 g (99.1%) of methyl 2-propoxy-4-methoxybenzoate as a light yellow oil.

(b) A solution of methyl 2-propoxy-4-methoxybenzoate (59.84 g, 266.8 mmol) in 10% NaOH (250 ml) was refluxed for 1 hour. The solution was cooled, water (150 ml) was added and then concentrated HCl until a pH of 3 was obtained. The aqueous solution was extracted with CH_2Cl_2 (3X) and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The solid residue was recrystallized from CH_2Cl_2/hexane to afford 47.44 g (84.6%) of 2-propoxy-4-methoxybenzoic acid.

Following procedures substantially similar to those described in Preparation 8 there was obtained the following compounds illustrated in Preparations 34c-34g.

(c) 40.22 g (95%) of 2-propoxy-4-methoxy-N,N-diethyl-benzamide, from 2-propoxy-4-methoxybenzoic acid (33.56 g, 159.63 mmol), thionyl chloride (104.46 g, 878.0 mmol), dichloroethane (100 ml) rather than toluene, and a catalytic amount of DMF for step one; and diethylamine (28.02 g, 383.11 mmol) and dichloroethane (150 ml) rather than MDC for step two. The product was purified by a Kugelrohr distillation at 145°C and 1.5 mm Hg.

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(d) 10.23 g (78.8%) of 2-aminosulfonyl-4-methoxy-6-propoxy-N,N-diethylbenzamide, from 2-propoxy-4-methoxy-N,N-diethylbenzamide (10.00 g, 37.69 mmol), sec-butyllithium (32.7 ml, 39.57 mmol), TMEDA (4.37 g, 37.69 mmol), THF (500 ml), sulfur dioxide (35 ml), hydroxylamine-O-sulfonic acid (13.21 g, 116.84 mmol) and NaOH (4.67 g, 116.84 mmol).

(e) 9.14 g (91.4%) of the diethylammonium salt of 4-propoxy-6-methoxysaccharin, m.p. 146-148°C, from 2-aminosulfonyl-4-methoxy-6-propoxy-N,N-diethylbenzamide (10.00 g, 29.03 mmol) and glacial acetic acid (100 ml), after recrystallization of the product from CH_2Cl_2/-hexane.

(f) 8.08 g (88.4%) of 2-phenylthiomethyl-4-propoxy-6-methoxysaccharin as a white crystalline solid, m.p. 117-118°C, from the diethylammonium salt of 4-propoxy-6-methoxysaccharin (8.00 g, 23.23 mmol), chloromethylphenyl sulfide (5.53 g, 34.84 mmol), TBAB (0.748 g, 2.32 mmol) and DMF (100 ml) rather than toluene. The reaction mixture was heated at 70-85°C for 23 hours and the product thus obtained was purified by column chromatography on silica eluting with 20% ethyl acetate/hexane.

(g) 5.88 g (95.9%) of 2-chloromethyl-4-propoxy-6-methoxysaccharin as a light yellow solid, m.p. 140-141°C, from 2-phenylthiomethyl-4-propoxy-6-methoxysaccharin (7.54 g, 19.16 mmol), sulfuryl chloride (3.10 g, 22.99 mmol) and CH_2Cl_2 (200 ml).

35. Preparation of 2-chloromethyl-4,6-diethoxy-saccharin [IV; R^4=EtO; R^5=6-EtO; X=Cl]

(a) To a mixture of aluminum chloride (68.0 g, 511.3 mmol) in dichloroethane (250 ml) under N_2 was added diethylcarbamoylchloride (65.5 g, 481.9 mmol) over 40 minutes while maintaining the reaction temperature at 10°C or below. The reaction mixture was warmed to room temperature over 30 minutes and then 1,3-diethoxybenzene

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50.0 g, 301.2 mmol) was added. The mixture was warmed to 45°C and stirred for 3 hours at this temperature and then at room temperature for 12 hours. The reaction mixture was poured into a mixture of water (500 ml) and ice, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (300 ml, 2X); and the organic extracts were combined, washed with water (150 ml) and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by a kugelrohr distillation at 140°C to afford 61.56 g of crude product as an oil which crystallized on standing. The solid product was recrystallized (2X) from 20% ethyl acetate/-hexane to afford 22.6 g of 2,4-diethoxy-N,N-diethyl-benzamide [V] as a white solid, m.p. 45-56°C.

Following procedures subtantially similar to those described in Preparation 8, paragraphs 2 and 3, there was obtained the following compounds illustrated in preparations 35b-35e.

(b) 10.38 g (80%) of 2-aminosulfonyl-4,6-diethoxy-N,N-diethylbenzamide, m.p. 141-143°C, from 2,4-diethoxy-N,N-diethylbenzamide (10.0 g), sec-BuLi (45.96 ml 0.9 M solution), TMEDA (5.67 ml), THF (400 ml), sulfur dioxide (50 ml), hydroxylamine-O-sulfonic acid (12.76 g) in water (100 ml) and NaOH (4.5 g) in water (25 ml).

(c) 8.89 g (95%) of the diethylammonium salt of 4,6-di-ethoxysaccharin, from 2-aminosulfonyl-4,6-diethoxy-N,N-diethylbenzamide (9.38 g) and glacial acetic acid (100 ml).

(d) 6.77 g (85%) of 2-phenylthiomethyl-4,6-diethoxy-saccharin, m.p. 122.5-123.5°C, from the diethylammonium salt of 4,6-diethoxysaccharin (7.0 g, 20.35 mmol), chloromethylphenyl sulfide (4.52 g, 28.49 mmol),TBAB (0.65 g, 2.03 mmol) and toluene (200 ml). The reaction mixture was heated at reflux for 15 hours, and the product thus obtained was purified by column

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chromatography on silica eluting with 30% ethyl acetate/hexane.

(e) 5.12 g (94%) of 2-chloromethyl-4,6-diethoxysaccharin, m.p. 159-161°C, from 2-phenylthiomethyl-4,6-diethoxysaccharin (6.67 g, 16.97 mmol), sulfuryl chloride (3.2 g, 23.70 mmol) and CH_2Cl_2 (200 ml).

36. Preparation of benzyl 4-hydroxybutyrate

To a suspension of the sodium salt of 4-hydroxybutyric acid (12.6 g, 0.1 mol) in DMF (400 ml) was added benzyl bromide (11.9 ml, 0.1 mol) and the mixture was stirred for 24 hours at room temperature. The reaction mixture was then poured into ice-water and was extracted with ether (3 X 300 ml). The organic layers were combined, washed with brine, dried and concentrated in vacuo. The residue thus obtained was purified by column chromatography on silica eluting with 20-50% ethyl acetate/hexane to afford 14.0 g of the desired product as an oil.

It is contemplated that other 4-R^4-R^5-2-halomethylsaccharins of Formula IV, useful as intermediates for the preparation of the compounds of Formula I, can be prepared as described hereinbelow in Preparations 37-39.

37. Preparation of 2-chloromethyl-4-[1-(trifluoromethyl)ethyl]saccharin [IV; R^4=CF_3CH_2; R^5=H; X=Cl]

Reaction of N,N-diethylbenzamide with sec-butyl lithium and TMEDA, followed by treatment of the resulting lithium salt with 2-iodo-1,1,1-trifluoroethane affords 2-(1,1,1-trifluoroethane)-N,N-diethylbenzamide. Reaction of the latter with lithium diisopropylamide, followed by treatment of the resulting lithium salt with methyl iodide affords 2-[1-(trifluoromethyl)ethyl]-N,N-diethylbenzamide. Following a procedure similar to that described in Preparation 5, reaction of the latter with sec-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium

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hydroxylamine-O-sulfonate affords 2-[1-(trifluoromethyl)ethyl]-6-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid, affords 4-[1-(trifluoromethyl)ethyl]saccharin. Reaction of the latter with paraformaldehyde and chlorotrimethylsilane in the presence of the stannic chloride in ethylene dichloride then affords the desired product.

38. Preparation of 2-chloromethyl-4-[1-(trichloromethyl)ethyl]saccharin.[IV; R^4=CCl_3CH_2; R^5=H; X=Cl]

Following a procedure substantially similar to that described in Preparation 37, but substituting 2-iodo-1,1,1-trichloroethane for 2-iodo-1,1,1-trifluoroethane the desired product can be prepared.

39. Preparation of 2-chloromethyl-4-(1,1-di-trifluoromethylmethyl)saccharin [IV; R^4=$(CF_3)_2CH$; R^5=H; X=Cl]

Reaction of benzoic acid with hexafluoroacetone in the presence of sec-butyl lithium affords 2-(1,1-ditrifluoromethyl-1-hydroxymethyl)benzoic acid, which can be deoxygenated to afford 2-(1,1-di-trifluoromethylmethyl)benzoic acid. Treatment of the latter with thionyl chloride affords 2-(1,1-di-trifluoromethylmethyl)benzoylchloride, which, on reaction with diethylamine, affords 2-(1,1-di-trifluoromethylmethyl)-N,N-diethylbenzamide. Following a procedure similar to that described in Preparation 5 reaction of the latter with sec-butyl lithium and reaction of the resulting lithium salt with sulfur dioxide followed by sodium hydroxylamine-O-sulfonate affords 2-(1,1-di-trifluoromethylmethyl)-6-aminosulfonyl-N,N-diethylbenzamide, which, on heating in glacial acetic acid affords 4-(1,1-di-trifluoromethylmethyl) saccharin [II]. Reaction of the latter with paraformaldehyde and chlorotrimethylsilane in the presence of stannic chloride in ethylene dichloride affords the desired product.

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40. Preparation of benzyl bromodifluoroacetate

It is contemplated that treatment of ethyl bromodifluoroacetate with sodium hydroxide, followed by treatment of the sodium salt of the resulting acid with benzyl bromide will afford the desired product.

41. Preparation of benzyl trichloroacetate

It is contemplated that treatment of ethyl trichloroacetate with sodium hydroxide, followed by treatment of the sodium salt of the resulting acid with benzyl bromide will afford the desired product.

42. Preparation of 2-isopropyl-4-methoxylbenzoic acid.

To a mixture of 1-bromo-2-isopropyl-4-methoxybenzene (6.5 g, 30 mmol) in THF (50 ml) at -78°C was added t-butyl lithium (20 ml, 1.7 M solution, 36 mmol) over 30 minutes. The mixture was stirred for 1 hour, then carbon dioxide was bubbled into the mixture for 15 minutes. The mixture was then stirred at room temperature for 2 hours, and was then added to ether and washed with 1M NaOH (50 ml). The organic layer was dried over $MgSO_4$, the solution was filtered and the solvent was removed in vacuo to afford unreacted starting material. The basic aqueous layer was acidified with 3N HCl and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4, filtered, and the solvent was concentrated in vacuo to afford 2.392 g of the desired product.

43. Preparation of 2-isopropyl-4,5-dimethoxybenzoic acid

Following a procedure substantially similar to that described in Preparation 42, there was obtained 2.52 g of the desired product from 1-bromo-2-isopropyl-4,5-dimethoxybenzene (20 mmol), THF (40 ml), t-butyl lithium (25 ml, 1.7 M solution) and carbon dioxide.

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44. Preparation of 2,6-dimethyl-4-[2-(4-morpholinyl)-ethoxy]benzoic acid.

(a) A mixture of methyl 2,6-dimethyl-4-hydroxybenzoate (6 mmol), 4-(2-chloroethyl)morpholine (7.2 mmol), K_2CO_3 (20 mmol) and DMF (15 ml) was heated at 50°C for 48 hours. The mixture was poured into water, extracted with ethyl acetate, and the organic layer was washed with water (3X). The organic layer was dried, filtered and concentrated in vacuo to afford 2.0 g of the desired product.

(b) A mixture of methyl 2,6-dimethyl-4-[2-(4-morpholinyl)ethoxy]benzoate (2.0 g), 3M NaOH (5 ml) and methanol (10 ml) was refluxed for 48 hours. The solution was neutralized with acetic acid and the solvents were removed in vacuo. Ethanol was added and the solvent was again removed in vacuo (2X) to afford a crude while solid. The solid was taken up in CH_3CN and precipitated with ether to afford 2.8 g of the desired product.

45. Preparation of 2,6-dimethyl-3-[2-(4-morpholinyl)-ethoxy]benzoic acid

(a) To a suspension of 80% NaH (2.38 g, 0.0992 mol) in THF (50 ml) was added dropwise methyl 2,6-dimethyl-3-hydroxybenzoate (7.122 g, 0.0396 mol) in THF (30 ml) at 20°C. The mixture was stirred for 20 minutes, then 4-(2-chloroethyl)morpholine hydrochloride (8.835 g, 0.0475 mol) was added over 15-20 minutes. The reaction mixture was stirred for 1 hour and then was heated to reflux overnight. The mixture was cooled to room temperature, poured into cold water and extracted with ethyl acetate (3X). The combined organic layers were washed with water (2X), dried over $MgSO_4$ and concentrated in vacuo to afford an oil. Hexane (100 ml) was added to the oil, the mixture was filtered through celite and the solvent was removed in vacuo to afford

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8.83 g (76%) of methyl 2,6-dimethyl-3-[2-(4-morpholinyl)ethoxy]benzoate as an orange oil.

(b) To a solution of methyl 2,6-dimethyl-3-[2-(4-morpholinyl)ethoxy]benzoate (8.83 g, 0.030 mol) in methanol (100 ml) was added NaOH (2.6 g, 0.063 mol) in water (20 ml). The mixture was heated to reflux for 96 hours and then additional methanol (100 ml) was added. The organic layer was separated from an oil layer, and the organics were treated with charcoal and filtered through celite. The solvent was removed in vacuo and the oily residue was washed with ether (3X). The oily residue was then dried in vacuo to afford a semi-solid, which was slurried with chloroform. The desired product was then collected by filtration to afford 5.5 g of the sodium salt of the desired product as a cream-colored solid.

46. Preparation of 2,6-dimethyl-3-[2-(1-pyrrolidinyl)ethoxy]benzoic acid

(a) Following a procedure substantially similar to that described in Preparation 45(a), there was obtained the desired product from methyl 2,6-dimethyl-3-hydroxybenzoate, THF, NaH, and 1-(2-chloroethyl)pyrrolidine.

(b) Following a procedure substantially similar to that described in Preparation 45(b), there was obtained the sodium salt of the desired product from methyl 2,6-dimethyl-3-[2-(1-pyrrolidinyl)ethoxy]benzoate, methanol and NaOH in water.

47. Preparation of 2-chloromethyl-4-ethoxy-6-methoxysaccharin [IV; R^4=EtO; R^5=6-MeO; X=Cl]

(a) Following a procedure substantially similar to that described in Preparation 33(a), there was obtained 1.22 g of crude 2-phenylthiomethyl-4-ethoxy-6-methoxysaccharin from 2-phenylthiomethyl-4-ethoxy-6-hydroxysaccharin (1.00 g, 2.74 mmol), triphenylphosphine (0.755 g, 2.88 mmol), methanol (0.092 g, 2.88 mmol) and diethylazodicarboxylate (0.524 g,

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3.01 mmol), after purification by column chromatography on silica eluting with 30% ethyl acetate/hexane.

(b) Following a procedure substantially similar to that described in Preparation 33(b), there was obtained 806 mg (96.2%) of the desired product from 2-phenylthiomethyl-4-ethoxy-6-methoxysaccharin (1.04 g, 2.74 mmol), sulfuryl chloride (0.309 ml, 3.84 mmol) and CH_2Cl_2.

48. Preparation of alcohols

It is contemplated that there can be prepared various alcohols of the formulae $HO-(CH_2)_n-(5-((CH_2)_n-N=B)-2-furanyl)$, $HO-(CH_2)_n-(5-((CH_2)_n-N=B)-2-thienyl)$ or $HO-(CH_2)_n-(5-((CH_2)_n-N=B)-1-R-2-pyrrolyl)$ by treatment of an appropriate aldehyde of formulae $HO-(CH_2)_n-(5-((CH_2)_nCHO)-2-furanyl)$, $HO-(CH_2)_n-(5-((CH_2)_nCHO)-2-thienyl)$ or $HO-(CH_2)_n-(5-((CH_2)_n-CHO)-1-R-2-pyrrolyl$, with an appropriate compound of formula HN=B, followed by reduction of the imine thus formed with sodium borohydride.

49. Preparation of further alcohols

It is contemplated that various alcohols of the formula $HO-(CH_2)_n-\equiv-(CH_2)_n-N=B"'$ can be prepared by the treatment of an alcohol of the formula $HO-(CH_2)_n-\equiv-H$ with an excess of sodium amide, followed by treatment of the anion thus formed with a compound of the formula $X(CH_2)_n-N=B"'$.

50. Preparation of further alcohols

It is contemplated that various alcohols of the formula $HO-(CH_2)_n-=-(CH_2)_n-N=B"$ can be prepared by the partial reduction of an alcohol of formula $HO-(CH_2)_n-\equiv-(CH_2)_n-N=B"'$ with palladium on barium sulfate which has been poisoned by the addition of quinoline.

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51. Preparation of benzyl 2,2-dimethyl-3-hydroxy-propionate

2,2-Dimethyl-3-hydroxypropionic acid (5.0 g, 42.37 mmol) was dissolved in methanol and treated with Cs_2CO_3 (6.9 g, 21.17 mmol) to afford the cesium salt of 2,2-dimethyl-3-hydroxypropionic acid which was dried under high vacuum for 3-4 hours. The cesium salt was then suspended in DMF (100 ml and treated with benzyl-bromide (8.11 g, 47.41 mmol). The mixture was stirred at room temperature for 15-16 hours and was then poured into ice-water and extracted with ethyl acetate (4X). The organic layers were combined, washed with water, then brine, and were dried. The solvent was removed in vacuo and the residue was purified by column chromatography on silica eluting with 35% ethyl acetate/hexane to afford 7.9 g (90%) of the desired product as an oil.

52. Preparation of N-(N,N-dimethylaminoethyl)-1-hydroxyacetamide

(a) A mixture of benzyloxyacetic acid (2.09 g, 12.58 mmol), thionyl chloride, N,N-dimethylethylene-diamine (2.33 g, 26.42 mmol) and DMF (2 drops) was refluxed under N_2 for 17 hours and then was stirred at room temperature overnight. The mixture was concentrated in vacuo, and the residue was taken up in ethyl acetate and washed with water, then brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford 2.39 g (80.5%) of N-(N,N-dimethyl-aminoethyl)-1-benzyloxyacetamide.

(b) To a solution of N-(N,N-dimethylaminoethyl)-1-benzyloxyacetamide (1.96 g, 8.29 mmol) in methanol was added methanolic·HCl (5 ml), followed by 10% palladium on carbon (0.800 g) at 0°C under N_2. The mixture was then placed on a Parr hydrogenator for 2 hours. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to afford a white crystalline

solid which was recrystallized from methanol/ether to afford 1.28 g (92.8%) of N-(N,N-dimethylaminoethyl)-2-hydroxyacetamide hydrochloride. The salt was then stirred in 90% acetone/methanol containing K_2CO_3 (600 mg) for 5 hours. The mixture was filtered and the filtrate was concentrated in vacuo to afford an oil. The oil was taken up in CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated in vacuo to afford the desired product as an oil.

13. Preparation of 2-chloromethyl-4-trifluoromethyl-6-methoxysaccharin. [IV; R^4=CF_3; R^5=6-MeO; X=Cl]

By a process substantially similar to that described in Preparation 6C, 2.3 g (6.492 mmol) of 6-aminosulfonyl-2-trifluoromethyl-4-methoxy-N,N-diethylbenzamide was cyclized in refluxing acetic acid (25 ml)/toluene (25 ml) to afford 2.38 g of the diethylammonium salt of 4-trifluoromethyl-6-methoxysaccharin. The latter (2.08) was then phenylthiomethylated with phenylthiomethyl chloride (0.64 ml, 6.77 mmol) in toluene (20 ml) in the presence of a catalytic amount of TBAB to afford 1.622 g (95%) of 4-trifluoromethyl-6-methoxy-2-phenylthiomethylsaccharin. The latter (0.8 g) was chlorinated with sulfuryl chloride (0.2 ml, 2.489 mmol) in CH_2Cl_2 (10 ml) to afford 0.65 g of the desired product.

The requisite benzamide was also obtained by procedures substantially similar to those described in Preparation 6C. Treatment of 1-trifluoromethyl-3-methoxybenzene (22.4 g, 123.4 mmol) with bromine (12.8 ml) in acetic acid at 60°C affords 2-trifluoromethyl-4-methoxy-1-bromobenzene. The latter, (1.9 g) on treatment with diethyl carbamyl chloride (11.6 ml, 92 mmol) in ether (500 ml) in the presence of n-BuLi (39 ml, 74.10 mmol) then affords 11.0 g (56%) of 2-trifluoromethyl-4-methoxy-N,N-diethylbenzamide,

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.p. 127-130 at 1 mm Hg. 8.1 g of the latter was then onverted into 2.1 g of the desired 6-aminosulfonyl-trifluoromethyl-4-methoxy-N,N-diethylbenzamide by reatment with TMEDA (11.1 ml, 73.57 mmol), s-BuLi 74 ml, 73.57 mmol), THF (225 ml), sulfur dioxide 50 ml), sulfuryl chloride (18 ml, 220.8 mmol) and monium hydroxide, and purification of the product by edium pressure chromatography eluting with 25% to 5% ethyl acetate/hexane.

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Preparation of the Final Products

Example 1A 4,6-dimethoxy-2-saccharinylmethyl 2,6-dichlorobenzoate [I; R^4=MeO; R^5=6-MeO; Ar=2,6-$Cl_2C_6H_3$]

A mixture of 0.5 g (0.0017 mol) 2-chloromethyl-4,6-dimethoxysaccharin, 0.33 g (0.0017 mol) 2,6-dichlorobenzoic acid and 17 g (0.25 ml, 0.0017 mol) triethylamine in 15 ml toluene was heated under reflux for about six hours, then cooled and concentrated to dryness in vacuo. The residue was chromatographed on silica gel, eluting with 40% ethyl acetate/hexane to give 0.44 g (53%) of the desired product, m.p. 200-201°C.

Following a procedure similar to that described in Example 1A above, the compounds of formula I listed in TABLE 1 below were similarly prepared. The reactions were carried out either in the presence of cesium carbonate, or potassium carbonate, as basic catalyst in an appropriate organic solvent as indicated in the column headed "Solv./Cat". The melting point of the product (in °C) and the recrystallization solvent are given in the column headed "m.p./solv.", and the yield, in %, of the product is given in the column headed "yield". In the examples the appropriate 4-R^4-R^5-2-chloromethylsaccharin was used as the starting material. Here and elsewhere in this specification various heterocyclic or other groups are abbreviated as follows:

Ac	acetyl
Mor	morpholinyl
pip	piperazinyl
Bzl	benzyl
azet	azetidinyl
imidazol	imidazolyl
pyr	pyrrolidinyl
pid	piperidinyl

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TABLE 1

Ex	R^4/R^5	Ar	Solv/Cat	m.p./Solv	Yield
1C	$CH(CH_3)_2$ 6-HO	$2,6\text{-}Cl_2C_6H_3$	DMF Cs_2CO_3	130-131	67(h) 80(i)
1BU	$CH(CH_3)_2$ 6-CH_3O	$2,6\text{-}Cl_2\text{-}3\text{-}BzlO\text{-}C_6H_2$	DMF K_2CO_3	139-140 MDC/hex	89

(h) The reaction was run at 80°C.
(i) The reaction was run at room temperature.

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Example 1AW 6-hydroxy-4-isopropyl-2-saccharinylmethyl 2,6-dichlorobenzoate [I; R^4=iPr; R^5=6-OH; Ar=2,6-$Cl_2C_6H_3$]

The cesium salt of 2,6-dichlorobenzoic acid was prepared from 4.48 g (0.0235 mol) of 2,6-dichlorobenzoic acid and 3.82 g (0.0117 mol) of Cs_2CO_3 in methanol. The salt was isolated by removing the solvent under reduced pressure and drying under high vacuum for 1/2 hr. The dried salt was suspended by stirring in 10-15 ml DMF and 3.4 g (0.0117 mol) 2-chloromethyl-6-hydroxy-4-isopropylsaccharin was added. The mixture was heated at 80° for 2-3 hr, cooled, diluted with water and extracted with 200 ml 7:3 ether:ethyl acetate. The organic layer was washed with water and saturated NaCl and dried. The solvent was removed and the residue was purified by flash chromatography with ethyl acetate-hexane on silica gel to give 4.53 (87%) of the desired product (no mp).

Example 2A. 4-isopropyl-2-saccharinylmethyl 2,6-dichloro-3-hydroxybenzoate [I; R^4=iPr; R^5=H; Ar=2,6-Cl_2,3-OHC_6H_2]

A solution of 1.4 g (0.0026 mol) 4-isopropyl-2-saccharinylmethyl 2,6-dichloro-3-benzyloxybenzoate in 50 ml ethyl acetate was treated with 0.3 g 10% palladium-on-charcoal and 0.5 ml acetic acid and the mixture stirred under 1 atm. of hydrogen for sixteen hours. The catalyst was removed by filtration, and the filtrate was taken to dryness in vacuo to give 1.16 g (100%) of the desired product, m.p. 78-80°C.

Example 2C. 4-isopropyl-6-methoxy-2-saccharinylmethyl 2,6-dichloro-3-hydroxybenzoate
[I; R^4=iPr; R^5=6-MeO; Ar=2,6-Cl_2,3-OHC_6H_2]

A mixture of 4-isopropyl-6-methoxy-2-saccharinylmethyl-2,6-dichloro-3-benzyloxybenzoate of Example 1BU (2.5 g, 4.4 mmol), 10% Pd on Carbon (0.7g) and glacial acetic acid (1 ml in ethyl acetate (100 ml)

was stirred under 50 psi hydrogen in a Parr hydrogenator for 1.5 hr. The resulting mixture was filtered through a pad of super cel eluting with ethyl acetate (100 ml). The combined filtrate was washed with saturated $NaHCO_3$, water, brine and dried. Removal of the solvent in vacuo and crystallization from 1:1 ether/hexanes gave 2.1 g (100%) of the desired product, mp 152-154°.

Example 4

By reaction of an appropriate 4-R^4-R^5-2-halomethylsaccharin of formula IV with an appropriate arylcarboxylic acid using the procedure described above in Example 1A, or by reaction of the appropriate saccharin of formula II with the appropriate chloromethyl benzoate using the procedure described in Example 11 below, the compounds of formula I listed in TABLE 2 below can be prepared.

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TABLE 2

Example	R^4	R^5	Ar
4CD	$CH(CF_3)(CH_3)$	H	$2,6\text{-}Cl_2C_6H_3$
4CE	$CH(CCl_3)(CH_3)$	H	$2,6\text{-}Cl_2C_6H_3$
4CF	$CH(CF_3)_2$	H	$2,6\text{-}Cl_2C_6H_3$

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Example 5A. 6-ethoxy-4-isopropyl-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-EtO; Ar=2,6-$Cl_2C_6H_3$]

To a solution of 500 mg (1.1 mmol) 6-hydroxy-4-isopropyl-2-saccharinylmethyl 2,6-dichlorobenzoate in 10-15 ml THF were added 298 mg (1.14 mmol) triphenylphosphine, 52 mg (1.13 mmol) ethanol and 198 mg (1.14 mmol) diethyl azodicarboxylate at RT. The mixture was stirred for 1 1/2 hr and then chromatographed on silica gel with 10% ethyl acetate in hexane to yield 370 mg (70%) of the desired product as a white powder, mp 140-141°C.

Example 7A. 6-(2-t-butoxy-2-oxoethoxy)-4-isopropyl-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-OCH_2(CO)Ot-Bu; Ar=2,6-$Cl_2C_6H_3$]

To a solution of 1.0 g (2.3 mmol) 6-hydroxy-4-isopropyl-2-saccharinylmethyl 2,6-dichlorobenzoate in 40 ml acetone at RT were added 0.62 g (4.5 mmol) anhydrous K_2CO_3 and 0.66 g (3.4 mmol) t-butyl bromoacetate. The mixture was stirred for 4-5 hr and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography to give 1.13 g (90%) of the desired product as a glass.

Example 7B. 6-(2-benzyloxy-2-oxoethoxy)-4-isopropyl-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-OCH_2(CO)OBzl; Ar=2,6-$Cl_2C_6H_3$]

In a similar manner the desired product was obtained as a glass in 61% yield from the 6-hydroxy compound and benzyl bromoacetate.

Example 11. 4-dimethylamino-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=NMe_2; R^5=H; Ar=2,6-$Cl_2C_6H_3$]

Following the procedure of preparation 18A, 5 g 2-bromo-N,N-dimethylaniline was converted to

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3.5 g N,N-diethyl-2-dimethylaminobenzamide. The amide was reacted by the method of preparation 18B to provide 65 mg 4-dimethylaminosaccharin, mp 228-229° from ether-hexane. A mixture of 11.1 g 2,6-dichlorobenzoyl chloride, 1.9 g paraformaldehyde and 0.1 g fused zinc chloride were heated at 100° for 2 hr and then vacuum distilled to yield 3.5 g chloromethyl 2,6-dichloro-benzoate collected above 145° at aspirator pressure which solidified on cooling, mp 70-72°. To a solution of 4-dimethylaminosaccharin and 0.1 ml diisopropyl-ethylamine in 1 ml dry acetonitrile was added 100 mg chloromethyl 2,6-dichlorobenzoate. The mixture was stirred at room temparature for 48 hrs and then at 50° for 24 hours, when tlc (MDC) showed complete reaction. The mixture was poured into EtOAc and extracted with saturated $NaHCO_3$ solution. The organic layer was dried and the solvent removed at reduced pressure. Chromatography in MDC yielded 15 mg of the desired product.

Example 12. 4-isopropyl-6-methoxy-2-saccharinylmethyl 2,6-dichloro-3-[2-(1-methyl-4-piperidinyl)ethoxy]-benzoate hydrochloride·1/2 hydrate

[I; R^4=iPr; R^5=6-MeO; Ar=2,6-Cl_2,3-OC_2H_4(1Me-4-pid)C_6H_2]

(a) To a mixture of 4-isopropyl-6-methoxy-2-saccharinylmethyl 2,6-dichloro-3-hydroxybenzoate (3.73 g, 7.8 mmol), 4-(2-hydroxyethyl)-1-carbobenzyloxypiperidine (1.92 g, 7.3 mmol), triphenylphosphine (2.27 g, 8.6 mmol) and THF at 0°C was added dropwise a solution of diethyl azodicarboxylate (1.5 g, 8.6 mmol) in THF. The mixture was stirred at 0°C under a nitrogen atmosphere for 1 hour and was then diluted with ether. The mixture was washed with 5% NaOH, water and then brine. The organic layer was concentrated in vacuo and the residue was purified by column chromatography on silica eluting with hexane/dichloromethane/ether (5/3/2) to afford 4.5 g (80%) of 4-isopropyl-6-methoxy-

2-saccharinylmethyl 2,6-dichloro-3-[2-(1-carbobenzyloxy-4-piperidinyl)ethoxy]benzoate.

(b) To a solution of 4-isopropyl-6-methoxy-2-saccharinylmethyl 2,6-dichloro-3-[2-(1-carbobenzyloxy-4-piperidinyl)ethoxy]benzoate (4.5 g, 6.2 mmol) in methanol/ethyl acetate (5/1) was added 37% aqueous formaldehyde (5 ml), followed by 10% palladium on carbon (1.0 g). The mixture was placed on a Parr hydrogenator at 50 psi for 6 h, additional 10% palladium on carbon (0.3 g) and 37% formaldehyde (2 ml) were added and the mixture was hydrogenated for another 4 hours. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was partitioned between methylene chloride/saturated $NaHCO_3$ (2/1, 250 ml), the layers were separated, and the organic phase was washed with water, then brine. The organic layer was dried, and the solvent was removed in vacuo to afford 1.3 g (35%) of 4-isopropyl-6-methoxy-2-saccharinylmethyl 2,6-dichloro-3-[2-(1-methyl-4-piperidinyl)ethoxy]benzoate. The product (1.3 g) was dissolved in dichloromethane/ether (1/1) and treated with ethereal HCl. The solution was diluted with ether (100 ml), chilled, sonicated and then allowed to stand for ten minutes. The solution was decanted and the residue was treated with ether, chilled, sonicated and allowed to stand as described above (2X). The solids that remained were slurried with ether, collected by filtration and dried at 45°C in vacuo to afford 0.6 g of the desired product as a white powder, m.p. 133-135°C.

Example 13. 4-isopropyl-6-methoxy-2-saccharinylmethyl 2,6-dichloro-3-[2-(4-methyl-1-piperazinyl)ethoxy]-benzoate dihydrochloride·3/4 hydrate·1/4 isopropanol

[I; R^4=iPr; R^5=6-MeO; Ar=2,6-Cl_2,3-OC_2H_4(4Me-1-pip)C_6H_2]

To a solution of 4-isopropyl-6-methoxy-2-saccharinyllmethyl 2,6-dichloro-3-hydroxybenzoate (1.42 g, 3.0 mmol), 1-(2-hydroxymethyl)-4-methyl-

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piperazine (0.47 g, 3.25 mmol) (Cymerman-Craig et al., Australian Journal Chemistry 1956, 89-94), triphenylphosphine (0.87 g, 3.3 mmol) in THF/dichloroethane (5/1) (30 ml) at 0°C was added diethylazodicarboxylate (0.57 g, 3.27 mmol) in dichloroethane (5 ml). When the addition was complete, a catalytic amount of dimethylaminopyridine was added and the mixture was warmed to room temperature and stirred overnight under argon. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica eluting with 5% methanol/dichloromethane to 10% methanol/dichloromethane to afford 0.63 g (34.8%) of 4-isopropyl-6-methoxy-2-saccharinylmethyl 2,6-dichloro-3-[2-(4-methyl-1-piperazinyl)ethoxy]benzoate. The product was dissolved in dichloromethane (3 ml) and treated with ethereal·HCl. The mixture was diluted with ether, sonicated and decanted. Additional ether was added to the residue and the precipitate which formed was collected by filtration and recrystallized from isopropanol to afford 0.53 g of the desired product as an off white powder, m.p. 151°C (dec.).

Example 14. 4-isopropyl-6-(1-(N,N-dibenzylamino-carbonyl)methoxy)-2-saccharinylmethyl 2,6-dichloro-benzoate

[I; R^4=iPr; R^5=6-OCH_2(CO-1,1-N,N-diNBzl$_2$); Ar=2,6-$Cl_2C_6H_3$]

A mixture of 4-isopropyl-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate (1.0 g, 225 mmol), N,N-dibenzyl-2-bromoacetamide (1.15 g, 3.6 mmol) and potassium carbonate (0.454 g, 2.7 mmol) in DMF was stirred at room temperature under N_2 for 17 hours. The DMF was removed in vacuo and the residue was taken up in ethyl acetate and washed with water (3X) and then brine. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo to afford a yellow

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oil. The oil was purified by column chromatography on silica eluting with 15% ethyl acetate/hexane followed by 30% ethyl acetate/hexane to afford 603 mg (39.3%) of the desired product as a white solid, m.p. 110-111.5°C.

Example 15. 4-ethoxy-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=EtO; R^5=6-OH; Ar=2,6-$Cl_2C_6H_3$]

A mixture of 2,6-dichlorobenzoic acid (1.702 g, 8.912 mol), cesium carbonate (1.423 g, 4.367 mmol) and methanol was stirred at room temperature under N_2 for 3 hours. The solvent was then removed in vacuo and the cesium salt of 2,6-dichlorobenzoic acid was dried under high vacuum for 2.5 hours. The salt was taken up in dry DMF and 2-chloromethyl-4-ethoxy-6-hydroxysaccharin (1.3 g, 4.456 mmol) was then added. The mixture was stirred at room temperature under N_2 for 40 hours, the solvent was removed in vacuo and the residue thus obtained was taken up in ethyl acetate. The organic layer was washed with water (3X), then saturated $NaHCO_3$ and was then dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography on silica eluting with 50% ethyl acetate/hexane to afford 1.481 g (74.4%) of the desired product as a white solid, m.p. 216-217°C.

Example 16. 4-ethoxy-6-[1-(5-dimethylaminomethyl-2-furanyl)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=EtO; R^5=6-OCH_2(2-furanyl-5$CH_2N(CH_3)_2$); Ar=2,6-$Cl_2C_6H_3$]

To a solution of 4-ethoxy-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate (0.625 g, 1.40 mmol) in THF under N_2 was added triphenylphosphine (0.386 g, 1.47 mmol), followed by 5-dimethylaminomethyl-2-hydroxymethylfuran (0.230 g, 1.48 mmol). Diethyl azodicarboxylate (0.268 g, 1.54 mmol) was then added to the reaction mixture and the solution was stirred at

room temperature for 17 hours. The solvent was removed in vacuo and the oil thus obtained was purified by column chromatography on silica eluting with 100% ethyl acetate to afford the desired product as a white solid, m.p. 157-158°C when recrystallized from ethyl acetate/hexane.

Example 17. 4-ethoxy-6-(1-(4-tert-butoxycarbonyl-1-piperazinylcarbonyl)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=EtO; R^5=6-OCH_2(4-t-BuOCO-1-pipCO); Ar=2,6-$Cl_2C_6H_3$]

A mixture of 4-ethoxy-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate (0.500 g, 1.12 mmol), K_2CO_3 (0.376 g, 2.24 mmol), DMF, and 1-(bromoacetyl)-4-(tert-butoxycarbonyl)piperazine (0.688 g, 2.24 mmol) (Arimoto et al., J. Antibiotics 1986, 39(9), 1243-1256) was stirred at room temperature for 17 hours. The solvent was removed in vacuo and the residue thus obtained was taken up in ethyl acetate and washed with water (3X) and then brine. The organic layer was dried and the solvent was removed in vacuo to afford a light brown oil. The oil was purified by column chromatography on silica eluting with 60% ethyl acetate/hexane and the residue thus obtained was crystallized from ethyl acetate to afford 219 mg (29.1%) of the desired product as a white crystalline solid, m.p. 193-195°C.

Example 18. 4-ethoxy-6-[2-(benzyloxy)ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=EtO; R^5=6-OC_2H_4(2-OBzl); Ar=2,6-$Cl_2C_6H_3$]

A mixture of 2-chloromethyl-4-ethoxy-6-[2-(benzyloxy)ethoxy]saccharin (0.900 g, 2.11 mmol), 2,6-dichlorobenzoic acid (0.604 g, 3.16 mmol), potassium carbonate (0.467 g, 3.38 mmol) and DMF was stirred at room temperature under N_2 for 17 hours. The solvent was removed in vacuo, and the residue thus obtained was

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extracted with ethyl acetate, washed with water (3X), saturated sodium bicarbonate, and finally brine. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by column chromatography on silica eluting with 30% ethyl acetate/hexane to afford an oil, which was crystallized from ethyl acetate/hexane to afford 0.766 g (62.5%) of the desired product as a white solid, m.p. 121-122°C.

Example 19. 4-ethoxy-6-[2-(hydroxy)ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=EtO; R^5=6-OC_2H_4(2-OH); Ar=2,6-$Cl_2C_6H_3$]

To a solution of 4-ethoxy-6-[2-(benzyloxy)-ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate (0.667 g, 1.15 mmol) in ethyl acetate was added 10% palladium on carbon (150 mg) and the mxiture was placed on a Parr hydrogenator at 50 psi for 3 hours. The catalyst was removed by filtration and the solvent was removed in vacuo to afford a colorless oil. The oil was crystallized from ethyl acetate/hexane to afford 417 mg (73.9%) of the desired product as a white solid, m.p. 166°C.

Example 20. 4-isopropyl-6-[1-(1,1-diphenylmethyl)-3-azetidinyloxy]-2-saccharinylmethyl 2,6-dichloro-benzoate

[I; R^4=iPr; R^5=6-(1,1-Ph_2CH)-3-azetO; Ar=2,6-$Cl_2C_6H_3$]

Following a procedure substantially similar to that described in Example 5A, there was obtained 633 mg (84.2%) of the desired product as a white solid, m.p. 205-207°C, from 4-iso-propyl-6-hydroxy-2-saccharinylmethyl 2,6-dichloro-benzoate (0.500 g, 1.13 mmol), THF (35 ml), triphenylphosphine (0.310 g, 1.18 mmol), 1-benzhydrylazetidin-3-ol (0.297 g, 1.24 mmol) (Anderson and Lok, J. Org. Chem. 1973, 37(24) 3953-3955) and diethyl azodicarboxylate (0.216 g,

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1.24 mmol); after purification of the final product by column chromatography on silica eluting with 30% ethyl acetate/hexane.

Example 23. 4-ethoxy-6-[1-(benzyloxycarbonyl)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=EtO; R^5=6-$OCH_2C(O)OBzl$; Ar=2,6-$Cl_2C_6H_3$]

A mixture of 4-ethoxy-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate (0.612 g, 1.37 mmol), K_2CO_3 (0.379 g, 2.74 mmol), and benzyl bromoacetate (0.426 g, 1.86 mmol) in acetone (40 ml) was stirred at room temperature under N_2 for 17 hours. The mixture was diluted with ether, filtered and the filtrate was concentrated in vacuo to a white gum. The gum was purified by column chromatography on silica eluting with 30% ethyl acetate/hexane and the residue was crystallized from ethyl acetate/hexane to afford 638 mg (78.4%) of the desired product as a white solid, m.p. 157-158.5°C.

Example 24. 4-ethoxy-6-[1-(carboxy)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=EtO; R^5=6-OCH_2(1-COOH); Ar=2,6-$Cl_2C_6H_3$]

To an ice-cold solution of 4-ethoxy-6-[1-(benzyloxycarbonyl)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate (0.560 g, 0.942 mmol) in ethyl acetate under N_2 was added 10% palladium on carbon (100 mg). The reaction mixture was then stirred under a hydrogen filled balloon for 2.5 hours, additional catalyst (150 mg) was added and stirring under a hydrogen atmosphere was continued for 17 hours. The catalyst was removed by filtration and the solvent was removed in vacuo to afford a colorless oil which crystallized under high vacuum. The solid was recrystallized from ethyl acetate/hexane to afford 417 mg (87.8%) of the desired product as a white solid, m.p. 179-180°C.

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Example 25. 4-isopropyl-6-(3-azetidinyloxy)-2-saccharinylmethyl 2,6-dichlorobenzoate methanesulfonate

[I; R^4=iPr; R^5=6-azetO; Ar=2,6-$Cl_2C_6H_3$]

To a solution of 4-isopropyl-6-[1-(1,1-diphenylmethyl)-3-azetidinyloxy]-2-saccharinylmethyl 2,6-dichlorobenzoate (0.584 g, 0.877 mmol) in methanol (45 ml) and ethyl acetate (15 ml) was added 10% palladium on carbon (100 mg). The reaction mixture was placed on Parr hydrogenator at 50 psi hydrogen pressure for 5 hours, additional catalyst (400 mg) was added and the mixture was placed back on the Parr hydrogenator for 2 hours. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to afford a colorless oil. The oil was treated with one equivalent of methanesulfonic acid in ethyl acetate, the solvent was removed in vacuo, and the gum thus obtained was triturated with ether. A white solid formed which was collected by filtration and dried for 10 hours on high vacuum to afford the desired product as an off-white solid.

Following a procedure substantially similar to that described in Example 5A, but substituting the appropriate alcohol for ethanol, there was obtained the following compounds of Formula I listed in Table 3A. Wherever available, the melting point (m.p.), recrystallization solvent, yield, and the solvent used for column chromatography on silica gel are given for each of the compounds in the columns headed "m.p./solv.", and "yield/chrom. solv.", respectively.

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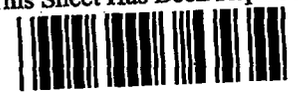


Table 3A

Example	R^4/R^5	Ar	m.p./solv.	Yield/chrom. solv.
26	$CH(CH_3)_2$ $6\text{-}OCH_2CH_2OBzl$	$2,6\text{-}Cl_2\text{-}C_6H_3$	115.5-116.5 --	75 35% EtOAc/hexane
27	$CH(CH_3)_2$ $6\text{-}O\text{-}[(CH_2)_2O]_3\text{-}(CH_2)_2OH$	$2,6\text{-}Cl_2\text{-}C_6H_3$	-- --	23 10% EtOAc/CH_2Cl_2
28	$CH(CH_3)_2$ $6\text{-}O\text{-}(CH_2)_3C(O)OBzl$	$2,6\text{-}Cl_2\text{-}C_6H_3$	gum	8 30% EtOAc/hexane
29	$CH(CH_3)_2$ 6-O-CH_2-(furan)-$N(CH_3)_2$	$2,6\text{-}Cl_2\text{-}C_6H_3$	154-156 --	22 10% EtOAc/CH_2Cl_2 to 3% EtOAc/CH_2Cl_2
30	$CH(CH_3)_2$ $6\text{-}OCH(CH_2OBzl)_2$	$2,6\text{-}Cl_2\text{-}C_6H_3$	gum --	64 30% EtOAc/hexane
31(a)	$CH(CH_3)_2$ $6\text{-}OCH_2C{\equiv}CCH_2N(Et)_2$	$2,6\text{-}Cl_2\text{-}C_6H_3$	gum --	40 50% EtOAc/hexane
32A	$CH(CH_3)_2$ $6\text{-}OCH_2C(CH_3)_2CO_2Bzl$	$2,6\text{-}Cl_2\text{-}C_6H_3$	foam --	55 25% EtOAc/hexane
32B	$CH(CH_3)_2$ $6\text{-}OCH_2C(O)NH(CH_2)_2N(CH_3)_2$	$2,6\text{-}Cl_2\text{-}C_6H_3$	foam --	48.2 7% MeOH/CH_2Cl_2

(a) Tributylphosphine was substituted for triphenylphosphine, and ether was substituted for THF.

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Example 34. 4-isopropyl-6-[(3-carboxy)propoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-OC_3H_6(3-COOH); Ar=2,6-$Cl_2C_6H_3$]

A mixture of 4-isopropyl-6-[3-(benzyloxycarbonyl)propoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate (1.2 g), ethyl acetate (60 ml) and 10% palladium on carbon (0.5 g) was placed under a hydrogen atmosphere on a Parr hydrogenator for 14 hours. The catalyst was removed by filtration through celite and the filtrate was concentrated in vacuo. This residue was treated with diethylamine to form the diethylamine salt of the product which was then passed through a column of silica eluting with 10-20% ethyl acetate/-CH_2Cl_2 to 10-30% methanol/CH_2Cl_2 to afford 0.68 g of the desired product as a foamy white solid.

Example 36. 4-isopropyl-6-[2-(hydroxy)ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-OC_2H_4(2-OH); Ar=2,6-$Cl_2C_6H_3$]

A mixture of 4-isopropyl-6-[2-(benzyloxy)-ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate (2.65 g), 10% palladium on carbon (0.8 g) and ethyl acetate/methanol (8/2, 300 ml) was placed on a Parr hydrogenator at 50 psi of hydrogen for 3 hours. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica eluting with 10% ethyl acetate/CH_2Cl_2 to afford 1.93 g (86%) of the desired product as a foamy white solid.

Example 37. 4-isopropyl-6-[2-(N,N-dimethylamino-methylcarbonyloxy)ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-OC_2H_4(2-OC(O)CH_2NMe_2); Ar=2,6-$Cl_2C_6H_3$]

To a mixture of 4-isopropyl-6-[2-(hydroxy)-ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate (1.31 g, 26.84 mmol) and N,N-dimethylglycine (0.29 g, 28.12 mmol) in CH_2Cl_2 (35 ml) was added 1,3-dicyclo-

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hexylcarbodiimide (1.65 g, 79.97 mmol), followed by 4-dimethylaminopyridine (0.29 g, 23.73 mmol). The mixture was stirred at room temperature for 24 hours and the solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica eluting with 20% methanol/CH_2Cl_2 and then a second column eluting with 100% ethyl acetate to afford 0.72 g of the desired product (labelled as Example 37a). The latter was dissolved in CH_2Cl_2 (25 ml) and treated with methanesulfonic acid (0.12 g, 0.082 ml) at 0°C to room temperature. The solvent was removed in vacuo to afford 0.81 g (96%) of the desired product as a foamy white solid (labelled as Example 37b).

Example 38. 4-isopropyl-6-(dimethylaminocarbonyloxy)-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-(OC(O)NMe_2) Ar=2,6-$Cl_2C_6H_3$]

To a mixture of 4-isopropyl-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate (0.5 g, 1.12 mmol) and DBU (0.17 g, 1.11 mmol) in THF at 0°C was added dimethyl carbamoyl chloride (0.12 g, 1.11 mmol). The mixture was stirred for 1/2 hour at 0°C and then at room temperature for 15 hours. The mixture was poured into water, extracted with ethyl acetate and the organic layer was washed with water and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography on silica eluting with CH_2Cl_2 to afford 0.22 g (38%) of the desired product as a foamy white solid.

Example 39. 4-isopropyl-6-[1-(carboxy)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-OCH_2(COOH); Ar=2,6-$Cl_2C_6H_3$]

6-(2-t-Butoxy-2-oxoethoxy)-4-isopropyl-2-saccharinylmethyl 2,6-dichlorobenzoate (0.94 g) was dissolved in a solution of CH_2Cl_2 (30 ml) and trifluoro-

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acetic acid (20 ml) and the mixture was stirred at room temperture for 6-7 hours. The solvent was removed in vacuo and any residual trifluoroacetic acid (was removed by co-distillation with CH_2Cl_2, ether and methanol. The residue thus obtained was dissolved in ether and was treated with an excess of triethylamine. After standing for 1-2 hours the triethylamine salt precipitated out of solution and was collected by filtration and recrystallized from CH_2Cl_2/hexane to afford 0.64 g (63%) of the triethylamine salt of the desired product as a white powder, m.p. 136-137°C.

Example 40. 4-isopropyl-6-[1-(carboxy)methoxy]-2-saccharinylmethyl 2,6-di-chlorobenzoate

[I; R^4=iPr; R^5=6-OCH_2(COOH); Ar=2,6-$Cl_2C_6H_3$]

Following a procedure substantially similar to that described in Example 39, but substituting diethylamine for triethylamine, there was obtained 2.61 g of the diethylamine salt of the desired product m.p. 155.5-157°C, from 6-(2-t-butoxy-2-oxoethoxy)-4-isopropyl-2-saccharinylmethyl 2,6-di-chlorobenzoate (4.3 g), and CH_2Cl_2/trifluoroacetic acid (140 ml, 1/1).

Example 41. 4-isopropyl-6-[(1-carboxy)difluoromethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-OCF_2(COOH); Ar=2,6-$Cl_2C_6H_3$]

It is contemplated that treatment of benzyl bromodifluoroacetate with 4-isopropyl-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate in DMF in the presence of potassium carbonate will afford 4-isopropyl-6-[1-(benzyloxycarbonyl)difluoromethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate, which upon treatment with 10% palladium on carbon in the presence of H_2 gas on a Parr hydrogenator affords the desired product.

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Example 42. 4-isopropyl-6-[(1-carboxy)dichloro-methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate.
[I; R^4=iPr; R^5=6-$OCCl_2(COOH)$; Ar=2,6-$Cl_2C_6H_3$]

It is contemplated that treatment of benzyl trichloroacetate with 4-isopropyl-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate in DMF in the presence of potassium carbonate will afford 4-isopropyl-6-[1-(benzyloxycarbonyl)dichloromethoxy]-2-saccharinyl-methyl 2,6-dichlorobenzoate, which upon treatment with 10% palladium on carbon in the presence of H_2 gas on a Parr hydrogenator affords the desired product.

Example 43. 4-isopropyl-6-[1-(dimethylaminoethyl-N-methylaminocarbonyl)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate
[I; R^4=iPr; R^5=6-$OCH_2(CONH(CH_2)_2N(CH_3)_2$; Ar=2,6-$Cl_2C_6H_3$]

(a) A mixture of 6-(2-benzyloxy-2-oxoethoxy)-4-isopropyl-2-saccharinylmethyl 2,6-dichlorobenzoate (1.037 g, 1.750 mmol), ethyl acetate and 10% palladium on carbon (500 mg) were stirred under a balloon filled with hydrogen gas for 3 hours. The catalyst was then removed by filtration and the solvent was removed in vacuo to afford 0.843 g (95.9%) of 4-isopropyl-6-[1-(carboxy)methoxy]-2-saccharinylmethyl 2,6-di-chlorobenzoate, m.p. 138-139.5°C.

(b) A mixture of 4-isopropyl-6-[1-(carboxy)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate (1.5 g, 2.99 mmol), thionyl chloride and DMF (2 drops) were refluxed for 2 hours under N_2. The solvent was then removed in vacuo and the residue was taken up in CH_2Cl_2. To this solution was added TMEDA (0.642 g, 6.28 mmol) and the mixture was stirred for 17 hours. The solvent was removed in vacuo and the residue was partioned between water (25 ml) and ethyl acetate (200 ml). The organic layer was separated, washed with 1% NaOH (3X) then brine, and it was then dried over Na_2SO_4. Removal of the solvent in vacuo, and purification of the residue

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by column chromatography on silica eluting with 10% methanol/CH_2Cl_2 affords 1.001 g (57.1%) of the desired product as a white foam.

Example 44. 4-isopropyl-6-[1-(4-methyl-1-piperazinylcarbonyl)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-OCH_2(4-Me-1-pipCO); Ar=2,6-$Cl_2C_6H_3$]

Following a procedure substantially similar to that described in Example 43(b), there was obtained 853 mg (73.3%) of the desired product as a white foam, from 4-isopropyl-6-[1-(carboxy)methoxy)-2-saccharinyl-methyl 2,6-dichlorobenzoate (1.00 g, 1.99 mmol), thionyl chloride, DMF (2 drops) and then CH_2Cl_2 and N-methyl-piperazine (0.419 g, 4.18 mmol); after purification of the product by column chromatography on silica eluting with 5% methanol/CH_2Cl_2.

Example 45. 1) 4-isopropyl-6-methoxy-2-saccharinyl-methyl 2,6-dichloro-3-[2-(1-methyl-3-pyrrolidinyl)-ethoxy]benzoate and

2) 4-isopropyl-6-methoxy-2-saccharinylmethyl 2,6-di-chloro-3-[2-(1-methyl-2-pyrrolidinyl)ethoxy]benzoate

1)[I; R^4=iPr;R^5=6-MeO;Ar=2,6-Cl_2,3-OC_2H_4(1-Me-3-pyr)C_6H_2]

2)[I; R^4=iPr;R^5=6-MeO;Ar=2,6-Cl_2,3-OC_2H_4(1-Me-2-pyr)C_6H_2]

Following a procedure substantially similar to that described in Example 13, but substituting 3-(2-hydroxyethyl)-1-methylpyrrolidine or 2-(2-hydroxy-ethyl)-1-methylpyrrolidine for 1-(2-hydroxyethyl)-4-methylpiperazine, it is contemplated that there can be prepared the above desired products.

Example 46. 4-isopropyl-6-(dimethylaminosulfonyloxy)-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-NMe_2SO_2O; Ar=2,6-$Cl_2C_6H_3$]

To a solution of 4-isopropyl-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate (1.0 g, 2.25 mmol) in THF which has been cooled in an ice-water bath was added DBU (0.47 ml, 3.37 mmol) followed by

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dimethylsulfamoyl chloride (0.36 ml, 3.34 mmol). The mixture was stirred with cooling for 1/2 hour, the cooling bath was then removed and the mixture was stirred at room temperature overnight. The reaction mixture was combined with the reaction mixture from a similar experimental run, but starting with 0.5 g of the 2,6-dichlorobenzoate, and the combined reaction mixtures were poured over ice-water and extracted with ethyl acetate. The organic layer was washed with water (15 ml, 3X), then brine, and was then dried and the solvent was removed in vacuo. The residue was purified by column chromatography on silica eluting with 50% CH_2Cl_2/hexane to afford 0.35 g (19%) of the desired product as a gum.

Example 47

Following a procedure substantially similar to that described in Example 5A, but substituting an appropriate alcohol, for example, benzyloxypoly-lower-alkylenehydroxy, $HO(CH_2O)_m$-A, HO-$(CH_2)_n$-(5-(($CH_2)_n$-N=B)-2-furanyl), HO-$(CH_2)_n$-(5-(($CH_2)_n$-N=B)-2-thienyl), HO-$(CH_2)_n$-(5-(($CH_2)_n$-N=B)-1-R-2-pyrrolyl), HO-$(CH_2)_n$-∫-$(CH_2)_n$-N=B"' or HO-$(CH_2)_n$-=-$(CH_2)_n$-N=B"', for ethanol, and if desired, an appropriately substituted 4-R^4-R^5-OH-2-saccharinylmethyl aryl carboxylate for 6-hydroxy-4-isopropyl-2-saccharinylmethyl 2,6-dichloro-benzoate, it is contemplated that there can be prepared various other compounds of the Formula I wherein R^5 is benzyloxypoly-lower-alkyleneoxy, -O-$(CH_2O)_m$A, -O-$(CH_2)_n$-(5-(($CH_2)_n$-N=B)-2-furanyl), -O-$(CH_2)_n$-(5-(($CH_2)_n$-N=B)-2-thienyl), -O-$(CH_2)_n$-(5-(($CH_2)_n$-N=B)-1-R-2-pyrrolyl), -O-$(CH_2)_n$-∫-$(CH_2)_n$-N=B"', or -O-$(CH_2)_n$-=-$(CH_2)_n$-N=B"'.

Example 48

Following a procedure substantially similar to that described in Example 23, but substituting an

appropriate compound of the formula $XC(R')_2COOR$ for benzyl bromoacetate and if desired, an appropriately substituted 4-R^4-R^5-OH-2-saccharinylmethyl aryl carboxylate for 4-ethoxy-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate, it is contemplated that there can be prepared various other compounds of the Formula I wherein R^5 is $-O-C(R')_2COOR$.

Example 49

Following a procedure substantially similar to that described in Example 24, but substituting an appropriate compound of the formula 4-R^4-R^5-$(O-C(R')_2COOCH_2C_6H_5)$-2-saccharinylmethyl aryl carboxylate for 4-ethoxy-6-[1-(benzyloxycarbonyl)-methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate, it is contemplated that there can be prepared various other compounds of the Formula I wherein R^5 is $-O-C(R')_2COOH$.

Example 50

Following a procedure substantially similar to that described in Example 37, but substituting, if desired, an appropriately substituted 4-R^4-R^5-(hydroxy-lower-alkoxy)-2-saccharinylmethyl aryl carboxylate for 4-isopropyl-6-[2-(hydroxy)ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate and an appropriate acid of formula $HOOC(CH_2)_n-N=B$ for N,N-dimethylglycine, it is contemplated that there can be prepared various other compounds of the Formula I wherein R^5 is $-O-(CH_2)_nOC(O)(CH_2)_n-N=B$.

Example 51

Following a procedure substantially similar to that described in Example 37, but substituting an appropriately substituted 4-R^4-R^5-(hydroxypoly-lower-alkyleneoxy)-2-saccharinylmethyl aryl carboxylate for 4-isopropyl-6-[2-(hydroxy)ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate and an appropriate acid of formula $HOOC(CH_2)_n-N=B$ for N,N-dimethylglycine, it is

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contemplated that there can be prepared various other compounds of the Formula I wherein R^5 is $-O-(CH_2)_n-O-(CH_2)_n-O-C(O)(CH_2)_n-N=B$.

Example 52

Following procedures substantially similar to those described in a) Example 17, but substituting, if desired, an appropriately substituted 4-R^4-R^5-OH-2-saccharinylmethyl aryl carboxylate for 4-ethoxy-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate and an appropriate halide of formula $X-(CH_2)_mC(O)N=B"$, wherein m is an integer from one to four, for 1-(bromoacetyl)-4-(tert-butoxycarbonyl)piperazine; or b) Example 38, but substituting, if desired, an appropriately substituted 4-R^4-R^5-OH-2-saccharinylmethyl aryl carboxylate for 4-isopropyl-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate and an appropriate compound of formula $X-(CH_2)_mC(O)N=B"$, wherein m is zero, for dimethylcarbamoyl chloride; or c) Example 43(b), but substituting, if desired, an appropriately substituted 4-R^4-R^5-(carboxy-lower-alkoxy)-2-saccharinylmethyl aryl carboxylate for 4-isopropyl-6-[1-(carboxy)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate and an appropriate compound of formula HN=B" for TMEDA, it is contemplated that there can be prepared various other compounds of Formula I wherein R^5 is $-O-(CH_2)_m-C(O)-N=B"$.

Example 53

Following a procedure substantially similar to that described in Example 46, but substituting sulfamoyl chloride for dimethylsulfamoyl chloride, and, if desired, an appropriately substituted 4-R^4-R^5-OH-2-saccharinylmethyl aryl carboxylate for 4-isopropyl-6-hydroxy-2-saccharinylmethyl 2,6-dichlorobenzoate, it is contemplated that there can be prepared various other compounds of Formula I wherein R^5 is aminosulfonyloxy.

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Example 54. 4-isopropyl-6-[2-(carboxy)-2,2-dimethyl-ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate

[I; R^4=iPr; R^5=6-$OCH_2CH(CH_3)_2$(2-COOH); Ar=2,6-$Cl_2C_6H_3$]

A mixture of 4-isopropyl-6-[2-(benzyloxy-carbonyl)-2,2-dimethylethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate (0.73 g) of Example 32A, ethyl acetate (40 ml) and 10% palladium on Carbon (0.2 g) was stirred under a hydrogen filled balloon for 2 hours. The mixture was filtered through celite and dried to afford 0.58 g (92%) of the desired product as a foam.

Example 55. 4-ethoxy-6-[2-(N,N-dimethylaminomethyl-carbonyloxy)ethoxy]-2-saccharinylmethyl 2,6-dichloro-benzoate

[I; R^4=EtO; R^5=6-$OC_2H_4OC(O)CH_2NMe_2$; Ar=2,6-$Cl_2C_6H_3$]

Following a procedure substantially similar to that described in Example 37, but substituting the compound of Example 19, for 4-isopropyl-6-[2-(hydroxy)-ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate, there was obtained the desired product (labelled as Example 55A), m.p. 112-114°C, after purification of the product by column chromatography on silica eluting with ethyl acetate (100%), followed by crystallization of the oil thus obtained from CH_2Cl_2/hexane. The free base was then converted into the methanesulfonic acid salt as described in Example 37 to afford the methansulfonate (labelled as Example 55B), m.p. 160-161°C after crystallization from CH_2Cl_2/hexane.

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BIOLOGICAL TEST RESULTS

Measurement of the inhibition constant, K_i, of a HLE-inhibitor complex has been described for truly reversible inhibition constants usually concerning competitive inhibitors. [Cha, Biochem. Pharmacol., 24, 2177-2185 (1975)]. The compounds of the present invention, however, do not form truly reversible inhibitor complexes but are consumed by the enzyme to some extent. Thus, instead of measuring a K_i, a K_i^* is calculated which is defined as the ratio of the k_{off}/k_{on}, the rate of reactivation of the enzyme to the rate of inactivation of the enzyme. The values of k_{off} and k_{on} are measured and K_i^* is then calculated.

The rate of inactivation, k_{on}, of enzymatic activity was determined for the compounds tested by measuring the enzyme activity of an aliquot of the respective enzyme as a function of time after addition of the test compound. By plotting the log of the enzyme activity against time, an observed rate of inactivation, k_{obs}, is obtained which can be represented as $k_{obs} = \ln 2/t_{1/2}$ where $t_{1/2}$ is the time required for the enzyme activity to drop by 50%. The rate of inactivation is then equal to

$$k_{on} = \frac{k_{obs}}{[I]}$$

where [I] is the concentration of the inhibiting compound.

The reactivation constant, k_{off}, is similarly determined, and the inhibition constant, K_i^*, is then calculated as

$$K_i^* = k_{off}/k_{on}$$

The values obtained for k_{on} and K_i^* for specific substituted saccharin derivatives are shown in TABLE 4, the compounds being identified by the Example numbers above where their preparations are described.

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TABLE 4

Example	k_{on} X 10^{-3} M^{-1} sec^{-1}	K^*_i (nM)
12b	320	0.031
14	--	0.09
16	--	0.058
17	--	0.1
18	--	0.27
20	--	2.2
23	--	0.52/0.4**
24	--	1.4/1.2**
25	82	0.14
26	--	0.07
27	--	3.8
29	180	0.038
30	1.3	3.3
31	--	0.050
32B	--	0.016
34	--	0.02
37a	235	0.02
37b	--	0.019
38	--	0.033
39	--	0.012
40	270	0.019
43b	--	0.016
44	--	0.029
46	--	0.058
54	297	0.052
55B	--	0.049

**The number represents K^*_i (nM) values for two separate experimental runs.

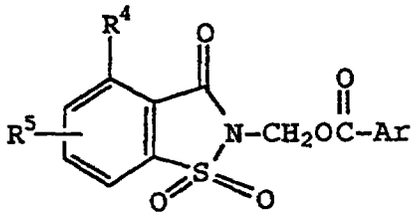
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CLAIMS:

1. A compound having the formula:



wherein:

1) Ar is halophenyl, halonaphthyl or haloanthryl substituted by from one to three, the same or different, members of the group consisting of -O-(alkylene)-1-lower-alkyl-4-piperidinyl, and -O-(alkylene)-1-lower-alkyl-2-or 3-pyrrolidinyl;

R^4 is hydrogen, halogen, lower-alkyl, perfluorolower-alkyl, perchlorolower-alkyl, polyfluoro-lower-alkyl, polychlorolower-alkyl, lower-alkenyl, lower-alkynyl, cyano, amino, lower-alkylamino, dilower-alkylamino, lower-alkoxy, benzyloxy, lower-alkoxy-carbonyl, phenyl or carboxamido; and

R^5 is hydrogen or from one to two the same or different substituents in any of the 5-, 6- or 7-positions selected from halogen, cyano, nitro, N=B, 1-lower-alkyl-2-pyrrolyl, lower-alkyl-sulfonylamino, polyfluorolower-alkyl-sulfonylamino, polychlorolower-alkylsulfonylamino, aminosulfonyl, lower-alkyl, poly-fluorolower-alkyl, polychlorolower-alkyl, cycloalkyl, lower-alkoxy, hydroxy, carboxy, carboxamido, hydroxy-lower-alkyl, methylenedioxy, cycloalkyloxy, formyl, aminomethyl, lower-alkyl-sulfonyl, polyfluorolower-alkylsulfonyl, polychloro-lower-alkylsulfonyl, lower-alkylsulfonylaminosulfonyl, lower-alkoxypoly-lower-alkyleneoxy, benzyloxypolylower-alkyleneoxy, hydroxy-poly-lower-alkyleneoxy, benzyloxy-lower-alkoxy,

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hydroxylower-alkoxy, polyhydroxylower-alkoxy or acetal or ketal thereof or said hydroxy groups of polyhydroxy-lower-alkoxy substituted by benzyl; poly(lower-alkoxy)-lower-alkoxy, -SR, -SOR, -SO_2R, -OCOR, -O-(alkylene)-COOR, -O-(alkylene)-COOH, -O-(alkylene)-N=B, -O-C(R')$_2$COOH, -O-C(R')$_2$-COOR, -O-C(X')$_2$COOH, -O-C(X')$_2$COOR, -O-$(CH_2)_n$OC(O)$(CH_2)_n$-N=B, -O-$(CH_2)_n$-O-$(CH_2)_n$OC(O)$(CH_2)_n$-N=B, -O-$(CH_2O)_m$-A, -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-2-furanyl), -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-2-thienyl), -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-1-R-2-pyrrolyl), -O-$(CH_2)_m$-C(O)-N=B", -O-$(CH_2)_n$-≡-$(CH_2)_n$-N=B"', -O-$(CH_2)_n$-=-$(CH_2)_n$-N=B"', aminosulfonyloxy, or dilower-alkylaminosulfonyloxy, wherein R is lower-alkyl, phenyl, benzyl, 1,1-diphenylmethyl, or naphthyl, or phenyl or napthyl substituted by from one to two substituents selected from lower-alkyl, lower-alkoxy or halogen; where N=B in each instance is amino, lower-alkylamino, dilower-alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl, carboxy-lower-alkylamino or -N-lower-alkyl-(alkylene-N(alkyl)$_2$; each R' group is independently hydrogen, or lower-alkyl; X' is chlorine or fluorine; n is an integer from one to four; m is an integer from zero to four; A is an azetidinyl, pyrrolidinyl, or piperidinyl ring attached through any available carbon atom, or said ring substituted on nitrogen by an R substitutent wherein R is as defined above; N=B" is amino, lower-alkylamino, dilower-alkylamino, dibenzylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 4-tert-butoxycarbonyl-1-piperazinyl,

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1-imidazolyl, or -NR"(alkylene)-N(alkyl)$_2$ wherein R" is hydrogen or lower-alkyl; and N=B"' is amino, lower-alkylamino, dilower-alkylamino, dibenzylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl, or -NR"(alkylene)-N(alkyl)$_2$ wherein R" is hydrogen or lower-alkyl;

or R^5 is a 5- or 6-membered saturated ring fused to the saccharin at the 5,6 or 6,7 positions, said ring containing two heteroatoms chosen from the group consisting of nitrogen, oxygen and sulfur or a methylated derivative of said ring;

or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof; or

2) Ar is phenyl, naphthyl or anthryl or such groups substituted by from one to three, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, perchlorolower-alkyl, lower-alkoxy, halogen, nitro, cyano, carboxy, PO(lower-alkoxy)$_2$, amino, lower-alkylamino, dilower-alkylamino, lower-alkanoylamino, lower-alkoxycarbonyl, hydroxy, benzyloxy, carboxy-lower-alkoxy, -SO$_2$-N=B, -CO-N=B, -(alkylene)-N=B, -COO(alkylene)-N=B, -NH(alkylene)-N=B; -N(lower-alkyl)-(alkylene)-N=B or -O-(alkylene)-N=B, where N=B is as defined above;

R^4 is as defined above; and

R^5 is from one to two, the same or different substituents in any of the 5-, 6-, or 7-positions selected from benzyloxypoly-lower-alkyleneoxy, hydroxy-poly-lower-alkyleneoxy, benzyloxylower-alkoxy, poly-hydroxylower-alkoxy in which the hydroxy groups are substituted by benzyl; -O-(alkylene)-COOH, -O-C(R')$_2$COOH, -O-C(R')$_2$COOR, -O-C(X')$_2$COOH, -O-C(X')$_2$COOR, -O-(CH$_2$)$_n$OC(O)(CH$_2$)$_n$-N=B,

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$-O-(CH_2)_n-O-(CH_2)_nOC(O)(CH_2)_n-N=B$, $-O-(CH_2O)_m-A$, $-O-(CH_2)_n-(5-((CH_2)_n-N=B)-2-furanyl)$, $-O-(CH_2)_n-(5-((CH_2)_n-N=B)-2-thienyl)$, $-O-(CH_2)_n-(5-((CH_2)_n-N=B)-1-R-2-pyrrolyl$, $-O-(CH_2)_m-C(O)-N=B"$, $-O-(CH_2)_n-\equiv-(CH_2)_n-N=B"'$, $-O-(CH_2)_n-=-(CH_2)_n-N=B"'$, aminosulfonyloxy, or dilower-alkylaminosulfonyloxy, wherein R, N=B, R', X', n, m, A, N=B" and N=B"' are as defined above;

or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof.

2. A compound as claimed in claim 1 wherein:

1) Ar is halophenyl, halonaphthyl or haloanthryl substituted by from one to three, the same or different, members of the group consisting of -O-(alkylene)-1-lower-alkyl-4-piperidinyl, and -O-(alkylene)-1-lower-alkyl-2-or 3-pyrrolidinyl;

R^4 is hydrogen, halogen, lower-alkyl, perfluorolower-alkyl, perchlorolower-alkyl, polyfluoro-lower-alkyl, polychlorolower-alkyl, lower-alkenyl, lower-alkynyl, cyano, amino, lower-alkylamino, dilower-alkylamino, lower-alkoxy, benzyloxy, lower-alkoxy-carbonyl, phenyl or carboxamido; and

R^5 is hydrogen or from one to two the same or different substituents in any of the 5-, 6- or 7-positions selected from halogen, cyano, nitro, N=B, 1-lower-alkyl-2-pyrrolyl, lower-alkyl-sulfonylamino, polyfluorolower-alkyl-sulfonylamino, polychlorolower-alkylsulfonylamino, aminosulfonyl, lower-alkyl, poly-fluorolower-alkyl, polychlorolower-alkyl, cycloalkyl, lower-alkoxy, hydroxy, carboxy, carboxamido, hydroxy-lower-alkyl, methylenedioxy, cycloalkyloxy, formyl, aminomethyl, lower-alkyl-sulfonyl, polyfluorolower-alkylsulfonyl, polychloro-lower-alkylsulfonyl, lower-alkylsulfonylaminosulfonyl, lower-alkoxypoly-lower-alkyleneoxy, benzyloxypolylower-alkyleneoxy, hydroxy-

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poly-lower-alkyleneoxy, benzyloxy-lower-alkoxy, hydroxylower-alkoxy, polyhydroxylower-alkoxy or acetal or ketal thereof or said hydroxy groups of polyhydroxy-lower-alkoxy substituted by benzyl; poly(lower-alkoxy)-lower-alkoxy, -SR, -SOR, -SO_2R, -OCOR, -O-(alkylene)-COOR, -O-(alkylene)-COOH, -O-(alkylene)-N=B, -O-C(R')$_2$COOH, -O-C(R')$_2$-COOR, -O-C(X')$_2$COOH, -O-C(X')$_2$COOR, -O-$(CH_2)_n$OC(O)$(CH_2)_n$-N=B, -O-$(CH_2)_n$-O-$(CH_2)_n$OC(O)$(CH_2)_n$-N=B, -O-$(CH_2O)_m$-A, -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-2-furanyl), -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-2-thienyl), -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-1-R-2-pyrrolyl), -O-$(CH_2)_m$-C(O)-N=B", -O-$(CH_2)_n$-≡-$(CH_2)_n$-N=B"', -O-$(CH_2)_n$-=-$(CH_2)_n$-N=B"', aminosulfonyloxy, or dilower-alkylaminosulfonyloxy, wherein R is lower-alkyl, phenyl, benzyl, 1,1-diphenylmethyl, or naphthyl, or phenyl or napthyl substituted by from one to two substituents selected from lower-alkyl, lower-alkoxy or halogen; where N=B in each instance is amino, lower-alkylamino, dilower-alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl, carboxy-lower-alkylamino or -N-lower-alkyl-(alkylene-N(alkyl)$_2$; each R' group is independently hydrogen, or lower-alkyl; X' is chlorine or fluorine; n is an integer from one to four; m is an integer from zero to four; A is an azetidinyl, pyrrolidinyl, or piperidinyl ring attached through any available carbon atom, or said ring substituted on nitrogen by an R substitutent wherein R is as defined above; N=B" is amino, lower-alkylamino, dilower-alkylamino, dibenzylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 4-tert-butoxycarbonyl-1-piperazinyl,

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1-imidazolyl, or -NR"(alkylene)-N(alkyl)$_2$ wherein R" is hydrogen or lower-alkyl; and N=B"' is amino, lower-alkylamino, dilower-alkylamino, dibenzylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl, or -NR"(alkylene)-N(alkyl)$_2$ wherein R" is hydrogen or lower-alkyl;

or R^5 is a 5- or 6-membered saturated ring fused to the saccharin at the 5,6 or 6,7 positions, said ring containing two heteroatoms chosen from the group consisting of nitrogen, oxygen and sulfur or a methylated derivative of said ring;

or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof.

3. A compound as claimed in claim 2 wherein Ar is 2,6-dichloro-3-[O-(alkylene)-1-lower-alkyl-4-piperidinyl]phenyl, 2,6-dichloro-3-[O-(alkylene)-1-lower-alkyl-2-pyrrolidinyl]phenyl, or 2,6-dichloro-3-[O-(alkylene)-1-lower-alkyl-3-pyrrolidinyl]phenyl.

4. A compound as claimed in claim 3 wherein Ar is 2,6-dichloro-3-[O-(alkylene)-1-lower-alkyl-4-piperidinyl)phenyl; R^4 is lower-alkyl; and R^5 is lower-alkoxy.

5. A compound as claimed in claim 4 wherein Ar is 2,6-dichloro-3-[O-(CH_2CH_2)-1-methyl-4-piperidinyl]phenyl.

6. 4-Isopropyl-6-methoxy-2-saccharinylmethyl 2,6-dichloro-3-[2-(1-methyl-4-piperidinyl)ethoxy]-benzoate, or an acid-addition salt thereof.

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7. A compound as claimed in claim 1 wherein:

Ar is phenyl, naphthyl or anthryl or such groups substituted by from one to three, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, perchlorolower-alkyl, lower-alkoxy, halogen, nitro, cyano, carboxy, PO(lower-alkoxy)$_2$, amino, lower-alkylamino, dilower-alkylamino, lower-alkanoylamino, lower-alkoxycarbonyl, hydroxy, benzyloxy, carboxylower-alkoxy, -SO_2-N=B, -CO-N=B, -(alkylene)-N=B, -COO(alkylene)-N=B, -NH(alkylene)-N=B; -N(lower-alkyl)-(alkylene)-N=B or -O-(alkylene)-N=B, where N=B in each instance is amino, lower-alkylamino, dilower-alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl, carboxy-lower-alkylamino or -N-lower-alkyl-(alkylene-N(alkyl)$_2$;

R^4 is hydrogen, halogen, lower-alkyl, perfluorolower-alkyl, perchlorolower-alkyl, polyfluoro-lower-alkyl, polychlorolower-alkyl, lower-alkenyl, lower-alkynyl, cyano, amino, lower-alkylamino, dilower-alkylamino, lower-alkoxy, benzyloxy, lower-alkoxy-carbonyl, phenyl or carboxamido; and

R^5 is from one to two the same or different substituents in any of the 5-, 6- or 7-positions selected from benzyloxypolylower-alkyleneoxy, hydroxy-poly-lower-alkyleneoxy, benzyloxylower-alkoxy, poly-hydroxylower-alkoxy in which the hydroxy groups are substituted by benzyl; -O-(alkylene)-COOH, -O-C(R')$_2$COOH, -O-C(R')$_2$-COOR, -O-C(X')$_2$COOH, -O-C(X')$_2$COOR, -O-$(CH_2)_n$OC(O)$(CH_2)_n$-N=B, -O-$(CH_2)_n$-O-$(CH_2)_n$OC(O)$(CH_2)_n$-N=B, -O-$(CH_2O)_m$-A, -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-2-furanyl), -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-2-thienyl), -O-$(CH_2)_n$-(5-($(CH_2)_n$-N=B)-1-R-2-pyrrolyl), -O-$(CH_2)_m$-C(O)-N=B", -O-$(CH_2)_n$-≡-$(CH_2)_n$-N=B"',

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$-O-(CH_2)_n-=-(CH_2)_n-N=B"'$, aminosulfonyloxy, or dilower-alkylaminosulfonyloxy, wherein R is lower-alkyl, phenyl, benzyl, 1,1-diphenylmethyl, or naphthyl, or phenyl or napthyl substituted by from one to two substituents selected from lower-alkyl, lower-alkoxy or halogen; N=B is as defined above; each R' group is independently hydrogen, or lower-alkyl; X' is chlorine or fluorine; n is an integer from one to four; m is an integer from zero to four; A is an azetidinyl, pyrrolidinyl, or piperidinyl ring attached through any available carbon atom, or said ring substituted on nitrogen by an R substitutent wherein R is as defined above; N=B" is amino, lower-alkylamino, dilower-alkylamino, dibenzylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 4-tert-butoxycarbonyl-1-piperazinyl, 1-imidazolyl, or $-NR"(alkylene)-N(alkyl)_2$ wherein R" is hydrogen or lower-alkyl; and N=B"' is amino, lower-alkylamino, dilower-alkylamino, dibenzylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 1-imidazolyl, or $-NR"(alkylene)-N(alkyl)_2$ wherein R" is hydrogen or lower-alkyl;

or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof.

8. A compound as claimed in claim 7 wherein:

Ar is phenyl, naphthyl or anthryl or such groups substituted by from one to three, the same or different, members of the group consisting of lower-alkyl, perfluorolower-alkyl, lower-alkoxy, halogen, nitro, $-PO(lower-alkoxy)_2$, lower-alkanoylamino, hydroxy, benzyloxy, carboxy-lower-alkoxy, $-SO_2-N=B$ or $-O-(alkylene)-N=B$, where N=B is dilower-alkylamino,

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1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, carboxylower-alkylamino or -N-lower-alkyl-(alkylene)-$N(alkyl)_2$; and

R^4 is hydrogen, primary or secondary lower-alkyl, lower-alkoxy or phenyl.

9. A compound as claimed in claim 8 wherein:

Ar is phenyl or phenyl substituted by from one to three, the same or different, members selected from the group consisting of lower-alkyl, lower-alkoxy, halogen, hydroxy, benzyloxy, carboxy-lower-alkoxy, $-SO_2-N=B$ or -O-(alkylene)-N=B, where N=B is dilower-alkylamino, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-lower-alkyl-1-piperazinyl, 4-benzyl-1-piperazinyl, carboxylower-alkylamino or -N-lower-alkyl-(alkylene)-$N(alkyl)_2$;

R^4 is primary or secondary lower-alkyl or lower-alkoxy; and

R^5 is hydroxypoly-lower-alkyleneoxy, benzyloxylower-alkoxy, polyhydroxylower-alkoxy in which the hydroxy groups are substituted by benzyl; -O-(alkylene)-COOH, $-O-C(R')_2COOH$, $-O-C(R')_2COOR$, $-O-(CH_2)_nOC(O)(CH_2)_n-N=B$, $-O-(CH_2O)_m-A$, $-O-(CH_2)_n-(5-((CH_2)_n-N=B)-2-furanyl)$, $-O-(CH_2)_m-C(O)-N=B"$, $-O-(CH_2)_n-\equiv-(CH_2)_n-N=B"'$, or dilower-alkylaminosulfonyloxy.

10. A compound as claimed in claim 9 wherein R^5 is one substituent in the 6-position selected from hydroxypoly-lower-alkyleneoxy, benzyloxylower-alkoxy, polyhydroxylower-alkoxy in which the hydroxy groups are substituent by benzyl; -O-(alkylene)-COOH, $-O-C(R')_2COOH$, $-O-C(R')_2COOR$, $-O-(CH_2)_nOC(O)(CH_2)_n-N=B$, $-O-(CH_2O)_m-A$, $-O-(CH_2)_n-(5-((CH_2)_n-N=B)-2-furanyl)$, $-O-(CH_2)_m-C(O)-N=B"$, $-O-(CH_2)_n-\equiv-(CH_2)_n-N=B"'$, or dilower-alkylaminosulfonyloxy, wherein R is benzyl;

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N=B is dilower-alkylamino; R' is hydrogen; n is an integer from one to four; m is an integer from zero to four; A is 3-azetidinyl ring or a 1-(1,1-diphenylmethyl)-3-azetidinyl ring; N=B" is dilower-alkylamino, dibenzylamino, 4-lower-alkyl-1-piperazinyl, 4-tert-butoxycarbonyl-1-piperazinyl, or -NR"(alkylene)-N(alkyl)$_2$ wherein R" is hydrogen, or lower-alkyl; and N=B"' is dilower-alkylamino.

11. A compound as claimed in claim 10 wherein:

Ar is 2,6-dichlorophenyl; and

R^4 is secondary lower-alkyl, or lower-alkoxy.

12. A compound as claimed in claim 11 selected from the group consisting of:

4-isopropyl-6-[1-(carboxy)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate;

4-isopropyl-6-[2-(benzyloxy)ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate;

4-isopropyl-6-[2-(dimethylaminomethyl-carbonyloxy)ethoxy]-2-saccharinylmethyl 2,6-dichloro-benzoate;

4-isopropyl-6-[3-(carboxy)propoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate;

4-isopropyl-6-[1-(5-dimethylaminomethyl-2-furanyl)methoxy]-2-saccharinylmethyl 2,6-dichloro-benzoate;

4-ethoxy-6-[1-(carboxy)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate;

4-ethoxy-6-[1-(5-dimethylaminomethyl-2-furanyl)methoxy]-2-saccharinylmethyl 2,6-dichloro-benzoate;

4-isopropyl-6-(dimethylaminocarbonyloxy)-2-saccharinylmethyl 2,6-dichlorobenzoate;

4-isopropyl-6-[1-(3-diethylamino-1-propynyl)-methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate;

4-isopropyl-6-[1-(dimethylaminoethyl-

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N-methylaminocarbonyl)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate;

4-isopropyl-6-[1-(4-methyl-1-piperazinyl-carbonyl)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate; and

4-isopropyl-6-[(2-carboxy-2,2-dimethyl)-ethoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate; or acid-addition salts of basic members thereof or base-addition salts of acidic members thereof.

13. 4-Isopropyl-6-[1-(carboxy)methoxy]-2-saccharinylmethyl 2,6-dichlorobenzoate, or a base-addition salt thereof.

14. A composition for the treatment of degenerative diseases which comprises a pharmaceutical carrier and an effective proteolytic enzyme inhibiting amount of a compound as claimed in any one of claims 1 to 13.

15. The use of a compound as claimed in any one of claims 1-13 for the preparation of a medicament for the treatment of degenerative diseases in a patient in need of such treatment.

This Sheet Has Been Replaced



