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PATENT SPECIFICATION

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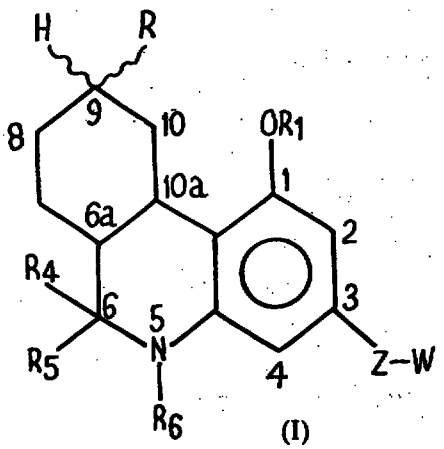
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(54) NOVEL QUINOLINE COMPOUNDS USEFUL IN THE PREPARATION OF HEXAHYDROBENZO [C] QUINOLINES

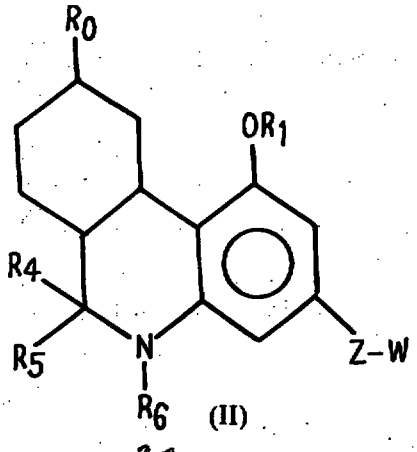
(71) We, PFIZER, INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235, 42nd Street, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to certain novel quinolines which are intermediates in the preparation of 1,9-dihydroxyoctahydrobenzo[c]quinolines, 1-hydroxyhexahydrobenzo[c]quinoline-9(8H)-ones and 1-hydroxy-tetrahydrobenzo[c]quinolines and derivatives thereof useful as CNS agents, especially as analgesics and tranquilizers, as hypotensives in mammals, including man, as agents for the treatment of glaucoma and as diuretics.

In our co-pending Application No. 20521/77 (Serial No. 1,579,228) certain benzo[c]quinolines; namely, 1,9-dihydroxyoctahydro-6H-benzo[c]quinolines (I), 1-hydroxyhexahydro-6H-benzo[c]quinoline-9(8H)-ones (II) and 1-hydroxy-tetrahydroquinolines (IV) have been found to be effective as CNS agents, especially as analgesics and tranquilizers, as hypotensives, which are non-narcotic and free of addiction liability, as agents for the treatment of glaucoma and as diuretics. Also included in our co-pending Application No. 20521/77 (Serial No. 1,579,228) are various derivatives of said compounds which are useful as dosage forms and precursors therefor. The above-named compounds and their derivatives have the formulae I, II and IV. Compounds of formulae III and IV are precursors to compounds of formulae II and I.

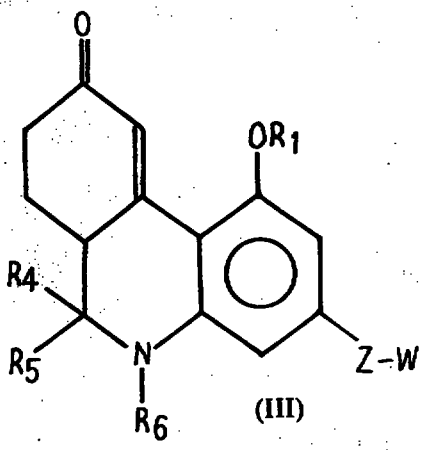


(I)



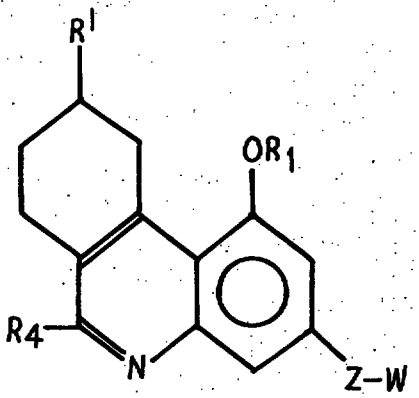
(II)

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(III)

and



(IV)

wherein R is selected from hydroxy, alkanoyloxy having from one to five carbon atoms and hydroxymethyl;

R_1 is selected from hydrogen, benzyl, benzoyl, alkanoyl having from one to five carbon atoms and $—CO—(CH_2)_p—NR_2R_3$ wherein p is 0 or an integer from 1 to 4; each of R_2 and R_3 when taken individually is selected from hydrogen and alkyl having from one to four carbon atoms; or R_2 and R_3 when taken together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring selected from piperidino, pyrrolo, pyrrolidino, morpholino and N-alkylpiperazino having from one to four carbon atoms in the alkyl group;

R_4 is selected from hydrogen, alkyl having from 1 to 6 carbon atoms and $—(CH_2)_z—C_6H_5$ wherein z is an integer from 1 to 4;

R_5 is selected from hydrogen, methyl and ethyl;

R_6 is selected from hydrogen, $—(CH_2)_y$-carbalkoxy having from one to four carbon atoms in the alkoxy group and y is 0 or an integer from 1 to 4; carbobenzyloxy, formyl, alkanoyl having from two to five carbon atoms, alkyl having from one to six carbon atoms; $—(CH_2)_x—C_6H_5$; and $—CO(CH_2)_{x-1}—C_6H_5$; wherein x is an integer from 1 to 4;

R_0 is selected from oxo, methylene and alkylenedioxy having from two to four carbon atoms;

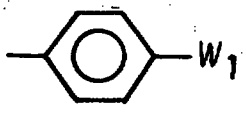
R' is selected from R and R_0;

Z is selected from:

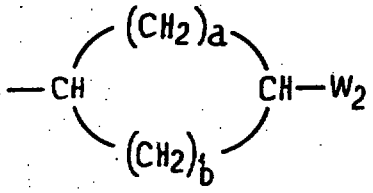
(a) alkylene having from one to nine carbon atoms;

(b) $—(alk_1)_m—X—(alk_2)_n—$ wherein each of (alk_1) and (alk_2) is alkylene having from one to nine carbon atoms, with the proviso that the summation of carbon atoms in (alk_1) plus (alk_2) is not greater than nine; each of m and n is 0 or 1; X is selected from O, S, SO and SO_2; and

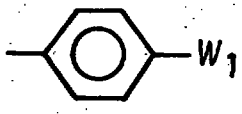
W is selected from hydrogen, methyl, pyridyl, piperidyl,



wherein W_1 is selected from hydrogen, fluoro and chloro; and



wherein W_2 is selected from hydrogen and



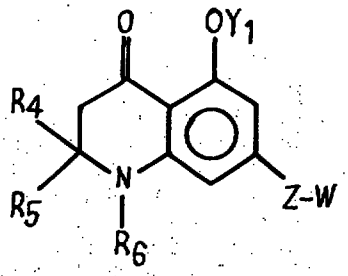
a is an integer from 1 to 5 and b is 0 or an integer from 1 to 5; with the proviso that the sum of a and b is not greater than 5; and the ketals of compounds of formulae II, III and IV wherein the ketal moiety has from two to four carbon atoms.

Also included in the invention described in co-pending Application No. 20521/77 (Serial No. 1,579,228) are pharmaceutically acceptable acid addition salts of compounds of formulae I and II. Representative of such salts are mineral acid salts such as the hydrochloride, hydrobromide, sulfate, nitrate, phosphate; organic acid salts such as the citrate, acetate, sulfosalicylate, tartrate, glycolate, malonate, maleate, fumarate, malate, 2-hydroxy-3-naphthoate, pamoate, salicylate, stearate, phthalate, succinate, gluconate, mandelate, lactate and methane sulfonate.

Compounds having the formulae I, II and III above contain asymmetric centers at the 6a- and/or 10a-positions. There may be additional asymmetric centers in the 3-position substituent (—Z—W), and 5-, 6- and 9-positions. Diastereomers with the 9β-configuration are generally favored over the 9α-isomers because of greater (quantitatively) biological activity. For the same reason, the trans(6a,10a)diastereomers of compounds of formula I are generally favored over the cis (6a,10a)diastereomers. As regards compounds of formula II, when one of R_4 and R_5 is other than hydrogen, the cis-diastereomers are preferred because of their greater biological activity. As regards formula IV compounds, asymmetric centers exist at the 9-position and in the 3-position substituents. Among the enantiomers of a given compound, one will generally be favored over the other and the racemate because of its greater activity. The enantiomer favored is determined by the procedures described herein. For example, the *l*-enantiomer of 5,6,6aβ,7,8,9,10,10aα - octahydro - 1 - acetoxy - 9β - hydroxy - 6β - methyl - 3 - (5 - phenyl - 2 - pentyloxy)benzo[c]quinoline is favored over the *d*-enantiomer and the racemate because of its greater analgesic activity. For convenience, the above formulae depict the racemic compounds. However, the above formulae are considered to be generic to and embracive of the racemic modifications of the compounds of this invention, the diastereomeric mixtures, the pure enantiomers and diastereomers thereof. The utility of the racemic mixtures, the diastereomeric mixtures as well as of the pure enantiomers and diastereomers is determined by the biological evaluations described below.

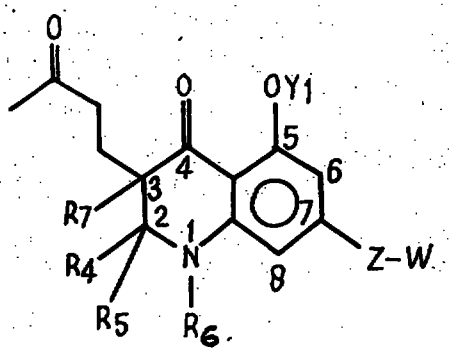
The present invention relates to an intermediate of the formula (V) useful in the preparation of compounds of formulae I, II, III and IV.

Our co-pending Application No. 35906/79 (Serial No. 1,579,230) is to intermediates of the formula (VII) which are useful in the preparation of compounds of formulae I, II, III and IV and which are prepared from the intermediates of the formula (V). The intermediates of the present invention have the formula:—



(V)

and the intermediates of our co-pending Application have the formula:—



(VII)

wherein

R_4, R_5, R_6 and Z—W are as defined above;

R_7 is selected from hydrogen and formyl; and

Y_1 is selected from hydrogen, methyl, ethyl and benzyl.

Asymmetric centers may exist in intermediates of formula V at the 2-position and in the 7-position substituent (—Z—W) and, of course, at other positions, e.g in the 1-position substituent. The 2- and 7-positions in formula V correspond to the 6- and the 3-positions, respectively, of compounds having formulae I, II, III and IV.

Favored, because of their greater biological activity relative to that of other compounds described herein, are compounds of formulae I and II where R and R_9 are as defined above;

R_1 is hydrogen or alkanoyl;

R_5 is hydrogen, methyl or ethyl;

and each of R_4 and R_6 is hydrogen or alkyl;

Z and W have the values shown below:

Z	m	n	W
alkylene having from 5 to 9 carbon atoms	—	—	H or CH_3
alkylene having from 2 to 5 carbon atoms	—	—	C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-pyridyl
$—(alk_1)_m—O—(alk_2)_n—$	1	1	C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-pyridyl
	0	1	
	1	0	
$—(alk_1)_m—O—(alk_2)_n—$	1	1	H or CH_3
	0	1	H or CH_3
	1	0	H or CH_3

Preferred compounds of formula I are those favored compounds described above wherein R represents hydroxy and which have the trans-configuration. Preferred compounds of formula II are those wherein R_9 is oxo.

Especially preferred are those preferred compounds of formulae I and II wherein:

R is hydroxy (formula I only);

R_1 is hydrogen or acetyl;

R_5 is hydrogen;

R_4 is methyl or propyl;

R_6 is hydrogen, methyl or ethyl;

when Z is alkylene having from 2 to 5 carbon atoms W is phenyl or 4-pyridyl;

when Z is $—(alk_1)_m—O—(alk_2)_n—$ wherein m is 0 and n is 1, $(alk_2)_n$ is alkylene having from four to nine carbon atoms, W is hydrogen or phenyl; and

when Z is alkylene having from five to nine carbon atoms, W is hydrogen.

The favored and preferred classes of intermediates of formula V are those compounds having said formulae which serve as intermediates for the favored and preferred compounds of formulae I and II as described above.

The compounds of this invention of formula V are prepared from appropriately substituted anilines, e.g., 3-hydroxy-5-(Z-W-substituted)-anilines (VIII) or derivatives thereof in which the 3-hydroxy group is protected by a group (Y_1) easily removable to regenerate the hydroxy group. Suitable protective groups are those which do not interfere with subsequent reactions of said 3-(protected hydroxy)-5-substituted anilines and which can be removed under conditions which do not cause undesired reactions at other sites of said compound or of products produced therefrom. Representative protective groups (Y_1) are methyl, ethyl, benzyl, substituted benzyl wherein the substituent is, for example, alkyl having from 1 to 4 carbon atoms, halo (Cl, Br, F, I), and alkoxy having from one to four carbon atoms.

The exact chemical structure of the protecting group is not critical to this invention since its importance resides in its ability to perform in the manner described above.

The selection and identification of appropriate protecting groups can easily

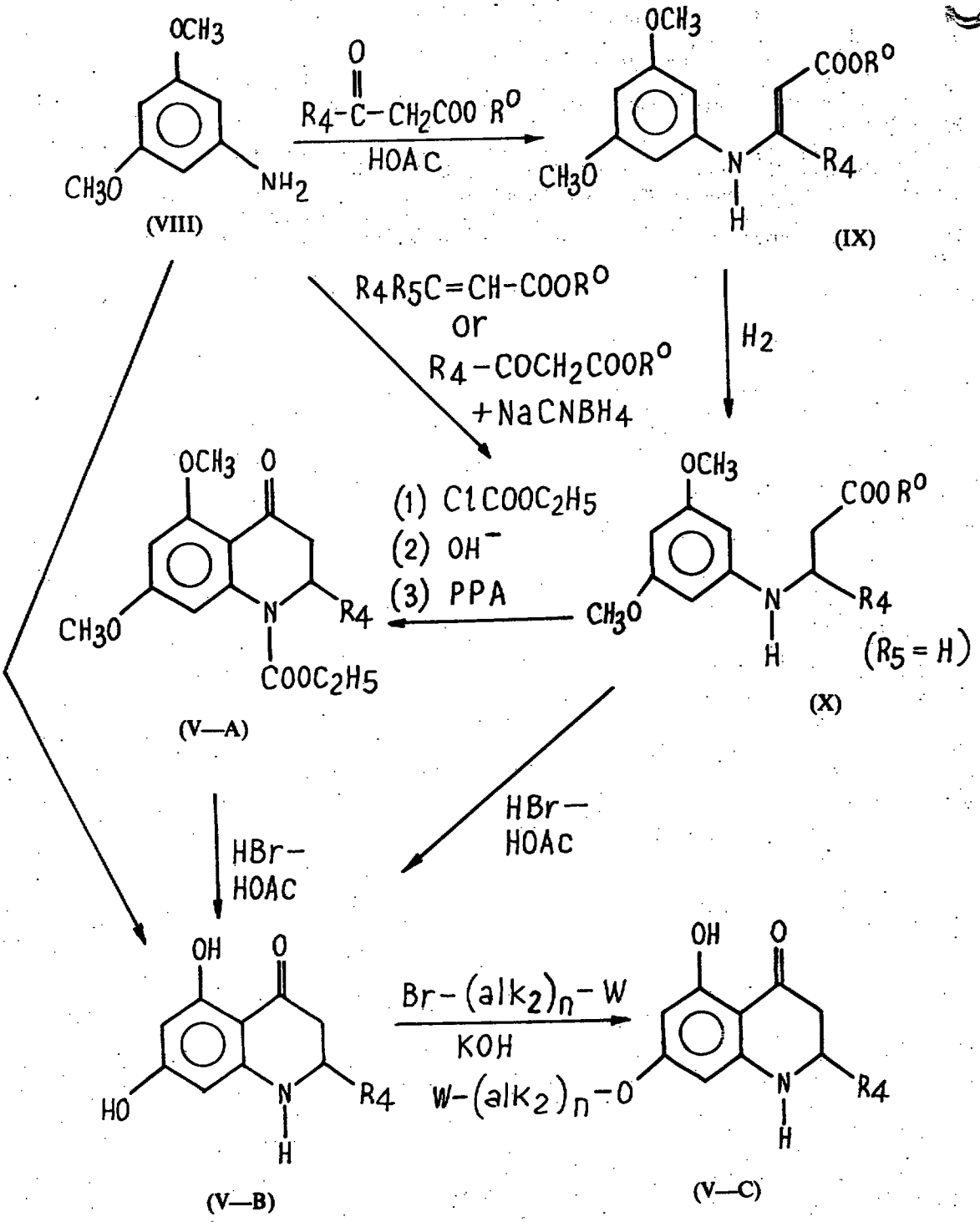
and readily be made by one skilled in the art. The suitability and effectiveness of a group as a hydroxy protecting group are determined by employing such a group in the above-illustrated reaction sequence. It should, therefore, be a group which is easily removed to permit restoration of the hydroxy groups. Methyl is favored as a protecting alkyl group since it is easily removed by treatment with pyridine hydrochloride. The benzyl group, also a favored protecting group, is removed by catalytic hydrogenolysis or acid hydrolysis.

When Z is $-(alk_1)_m-X-(alk_2)_n-$, Y_1 is preferably benzyl or a substituted benzyl group since it can subsequently be removed without detriment to the Z group.

The protected aniline derivative (VIII) is then converted to a compound of formula IX by known technology as described herein.

An abbreviated reaction sequence (Flow Sheet A) for preparing representative compounds of formula V beginning with a 3-(protected hydroxy)-5-(Z-W-substituted)aniline (VIII) wherein —Z—W is OCH_3 is given below:

Flow Sheet
A



R° in the above flow sheet represents alkyl having from one to six carbon atoms. (R_5, for the purpose of illustration in the overall Flow Sheet, is represented as hydrogen. However, in the sequence VIII → X or VIII → V—B, R_5 can be hydrogen, methyl or ethyl.)

The 5-substituent of formula VIII compounds can be group —Z—W desired in compounds of formulae II or I, or a group readily convertible to said group. When the Z moiety of group —Z—W is $—(alk_1)_m—X—(alk_2)_n—$ wherein X is O or S and each of m and n is 0, the 5-substituent, when W is hydrogen, is —XH (i.e., OH or SH) or a protected —XH group of the formula $—X—Y_1$ wherein Y_1 is as defined above. When, of course, —Z—W is $—(alk_1)_m—X—(alk_2)_n—W$ wherein m is 1, n is 0 and W is hydrogen, the 5-substituent becomes $—(alk_1)_m—X—H$. The —XH group is advantageously protected in the manner described above.

The appropriate 3-hydroxy-5-substituted anilines discussed above are reacted, preferably in the form of derivatives in which the 3-hydroxy group (and 5-hydroxy group if one is present) is protected as mentioned above in order to achieve satisfactory reactions, with an alkyl β-ketoester, e.g., an alkyl acetoacetate, in the presence of acetic acid to provide the corresponding β-[(3-protected hydroxy)-5-substituted anilino]-β-(R_4)-acrylate (IX). The reaction is generally conducted in a reaction-inert solvent such as benzene or toluene at temperatures of from about 50°C. to the reflux temperature of the solvent under conditions which result in removal of by-product water. Benzene and toluene are efficient solvents when the reaction is conducted at the reflux temperature, since they permit azeotropic removal of by-product water. Other means of water removal — or effective removal of water — such as molecular sieves can be employed, as can other solvents which permit azeotropic removal of water.

Favored protecting groups for the 3-hydroxy-5-substituted aniline reactants are methyl, ethyl and benzyl groups since the ethers are easily prepared, afford satisfactory yields of compounds of formulae IX and X and are conveniently removed.

The alkyl β-ketoester, preferably one in which the alkyl group has from one to six carbon atoms, is generally used in excess to insure maximum conversion of the aniline reactant to the corresponding alkyl β-anilino-β-(R_4)-acrylate (IX). Ten to twenty percent excess of alkyl β-ketoester is usually sufficient to achieve satisfactory conversions. Acetic acid is used in catalytic amounts to facilitate reaction.

The alkyl β-anilino-β-(R_4)-acrylate (IX) is then reduced to the corresponding alkyl-3-[(3-protected hydroxy)-5-substituted anilino]-3-(R_4)-propionate (X) by, for example, sodium borohydride-acetic acid and catalytic hydrogenation. A preferred catalyst is platinum dioxide since it conveniently permits the reaction to be carried out at low pressures, i.e., at pressures under 50 p.s.i. Other catalysts such as noble metals, e.g., platinum, palladium, rhodium, supported or unsupported, can be used along with pressures of hydrogen ranging from about atmospheric to super-atmospheric, e.g., 2000 p.s.i. In addition to such catalysts which are heterogeneous catalysts, this step can be carried out using homogeneous catalysts such as Wilkinson's catalyst, tris(triphenylphosphine)chlororhodium(I).

Of course, when the protecting group or groups are benzyl or substituted benzyl, catalytic hydrogenation will result in their removal. For this reason, methyl or ethyl groups are preferred as protecting groups for the 3- and/or 5-hydroxy groups of formula VIII reactants.

Alternatively, compounds of formula X can be prepared directly from compounds of formula VIII by reaction of formula VIII compounds with an alkyl 3,3-R_4R_5-acrylate in acetic acid. The reaction is conveniently carried out by reacting equimolar quantities of the alkyl 3,3-R_4R_5-acrylate and disubstituted aniline (VIII) in from 0.1 to 2 equivalents of glacial acetic acid at temperatures ranging from 0°C. to the reflux temperature.

Alternatively, compounds of formula V—B may be prepared directly by condensation of equimolar quantities of VIII with the appropriate substituted acrylic acid (R_4R_5C=CH—COOH) in pyridine hydrochloride at 150°—200°C.

In addition, when the R_4,R_5 groups are both alkyl, treatment of VIII and the alkyl R_4,R_5 acrylate in a reaction-inert solvent, e.g. tetrahydrofuran, with mercuric acetate followed by reduction with sodium borohydride gives X.

Direct conversion of compounds of formula VIII to compounds of formula X is also conveniently achieved by treating a 3,5-(diprotected hydroxy)aniline hydrochloride with an excess of an alkyl acetoacetate, e.g. ethyl acetoacetate, in the presence of sodium cyanoborohydride in a solvent such as methanol.

The alkyl 3-anilino-3-(R_4)-propionate (X) is then cyclized to the corresponding 2-(R_4)-quinolin-4-one (formula V—A or —B) by means of a suitable cyclizing agent such as polyphosphoric acid (PPA), hydrogen bromide-acetic acid, sulfuric acid, oleum (fuming sulfuric acid), hydrogen fluoride, trifluoroacetic acid, phosphoric

acid-formic acid and others known to those skilled in the art. In a modification of this conversion, the alkyl 3-anilino-3-(R_4)-propionate (X) can be converted to the corresponding acid by, for example, saponification of the ester followed by acidification, prior to cyclization.

The ether protecting, or blocking, groups on the 3-(and 5-)hydroxy groups can be removed at the time of cyclization through the use of hydrobromic acid in acetic acid as cyclizing agent and deblocking agent. Hydrobromic acid, 48% aqueous, is generally used since it affords satisfactory cyclization and deblocking. The reaction is conducted at elevated temperatures and desirably at the reflux temperature. However, when Z is $-(alk_1)_m-X-(alk_2)_n-$ cyclization conditions such as polyphosphoric acid or trifluoroacetic acid must be used to avoid cleavage of the ether or thioether linkage.

Alternatively, the protecting group (or groups) can be removed subsequent to the cyclization reaction. Hydrobromic acid-acetic acid is also a favored agent for deblocking at this stage of the overall synthesis. The reaction is carried out as described above.

Other reagents such as hydriodic acid, pyridine hydrochloride or hydrobromide can be used to remove protecting ether groups such as methyl and ethyl groups. When the protecting groups are benzyl or substituted benzyl groups, they can be removed by catalytic hydrogenolysis. Suitable catalysts are palladium or platinum, especially when supported on carbon. Alternatively, they can be removed by solvolysis using trifluoroacetic acid. Of course, when group —Z—W contains sulfur, acid debenzylation is used rather than catalytic debenzylation.

A favored method for the transformation of compounds of formula X to compounds of formula V which affords satisfactory yields and permits use of relatively mild conditions comprises conversion of formula X compounds to N-carbalkoxy derivatives wherein the N-carbalkoxy group has from two to five carbon atoms by reaction with the appropriate alkyl or benzyl chloroformate. The N-carbalkoxy or carbobenzyloxy derivative of formula X is then cyclized by means of a polyphosphoric acid to the corresponding N-carbalkoxy or carbobenzyloxy derivative of formula V compounds. The N-substituted derivatives of formula X compounds can, if desired, be hydrolyzed to the corresponding 3-[(N-substituted)-3-(protected hydroxy)-5-substituted anilino]-3-(R_4)-propionic acid prior to cyclization. Polyphosphoric acid generally produces maximum cyclization and is a preferred cyclizing agent.

Compounds of formula V in which the hydroxy group or groups are protected and in which the nitrogen atom is substituted with carbalkoxy are treated with hydrobromic acid-acetic acid to give compounds of formula V—B. When the hydroxy protecting group or groups are benzyl or substituted benzyl, regeneration of the hydroxy groups is accomplished by catalytic hydrogenolysis. A carbalkoxy group if present on the nitrogen atom is unchanged by this reaction. It can, if desired, be subsequently removed by treatment with hydrobromic acid-acetic acid or any of a variety of acids or bases. Removal of the benzyl protecting group by treatment with trifluoroacetic acid also removes any N-carbalkoxy group present.

When the —Z—W substituent of formula V compounds is —XH (X = O or S), and it is desired to have said —Z—W substituent represent, in compounds of formulae II or I, a group $-X-(alk_2)_n-W$ wherein X is O, S, SO or SO_2, and W is as previously defined, conversion of group —XH to group $-X-(alk_2)_n-W$ is conveniently and advantageously undertaken at this point in the overall reaction sequence. Thus, the 7—XH group of formula V—B above represented, for the purposes of illustration, as —OH, is transformed by the Williamson reaction with the appropriate bromide [$Br-(alk_2)_n-W$], mesylate or tosylate, to group $-O-(alk_2)_n-W$ (formula V—C).

Similarly, when group —Z—W of formula V is $-(alk_1)-X-H$, its conversion to $-(alk_1)-X-(alk_2)_n-W$ wherein n is 0 or 1 and W is other than hydrogen is conveniently undertaken at this stage of the reaction sequence via the Williamson reaction.

A variety of groups, such as those included within the definition of R_6, can be used in place of carbalkoxy or carbobenzyloxy in this favored method to mask the nitrogen against protonation.

Group R_6, if not already present in compounds of formulae V—A, V—B or V—C, can be introduced by reaction with the appropriate Cl—R_6 or Br—R_6 reactant according to known procedures.

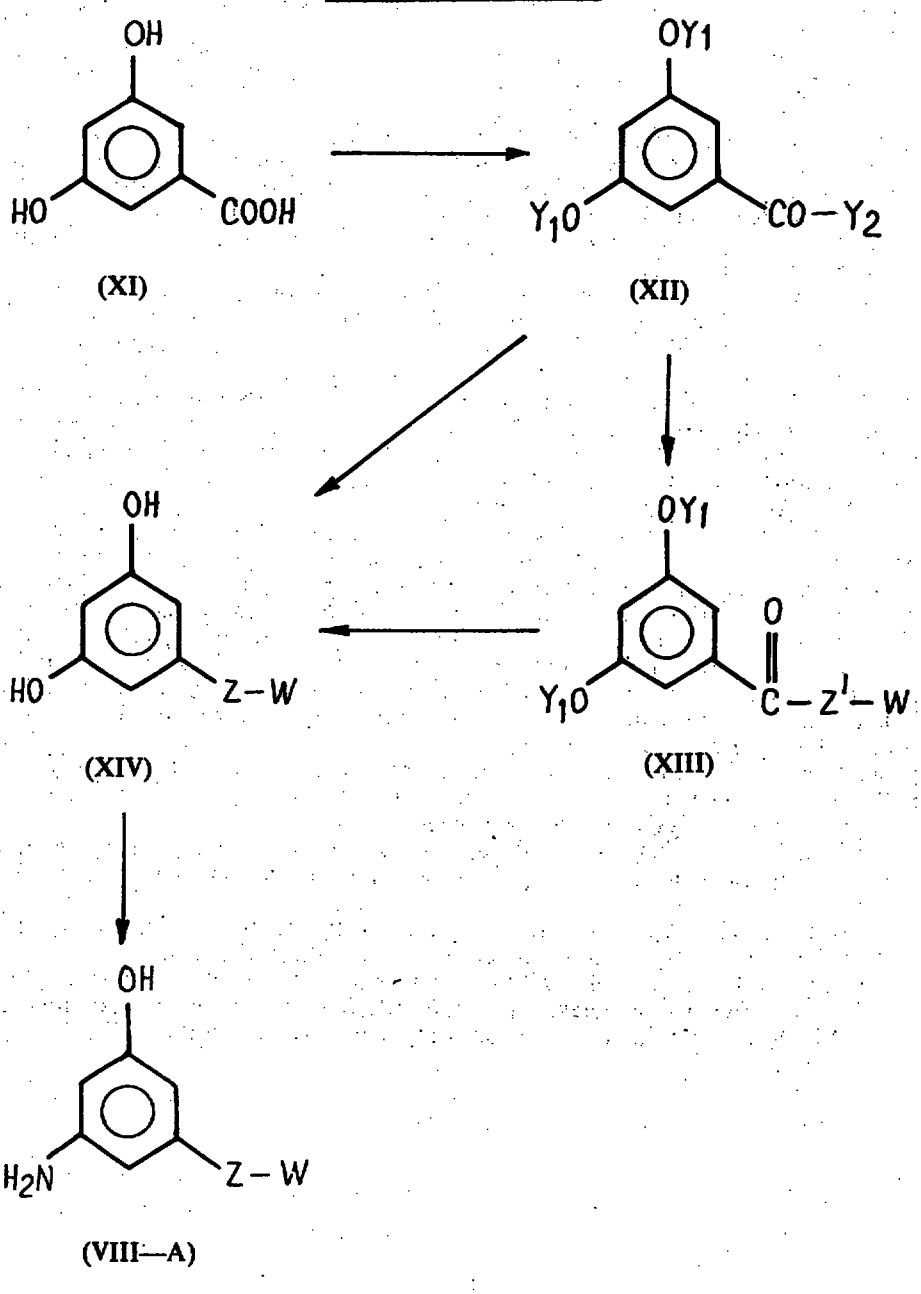
The 3-hydroxy-5-(Z—W-substituted)anilines are prepared from corresponding 5-(Z—W-substituted)resorcinols via the Bucherer Reaction which comprises

reacting the appropriate 5-(Z—W-substituted)resorcinol with aqueous ammonium sulfite or bisulfite. The reaction is conducted in an autoclave at elevated temperatures, e.g. from about 150° to about 230°C. The aniline product is isolated by acidifying the cooled reaction mixture and extracting the acid mixture with, for example, ethyl acetate. The acid solution is neutralized and extracted with a suitable solvent, e.g. chloroform, to recover the aniline product. Alternatively, the aniline product is isolated by extracting the cooled reaction mixture with an appropriate solvent followed by column chromatography of the crude product.

The 5-(Z—W-substituted)resorcinols, if not known are prepared from 3,5-dihydroxybenzoic acid. The procedure comprises esterifying 3,5-dihydroxybenzoic acid in which the hydroxy groups are protected (e.g., as methyl, ethyl or benzyl ethers); or alternatively, amidating the 3,5-[di(protected hydroxy)]benzoic acid.

The overall abbreviated sequence is illustrated below (Flow Sheet E):

Flow Sheet E



(XI) (XII) (XIV) (XIII) (VIII—A)

The starting material, 3,5-dihydroxybenzoic acid XI is converted to a compound of formula XII wherein Y_2 represents an alkoxy group, desirably methoxy or ethoxy for ease of preparation, or an amino group; and Y_1 is a hydroxy protecting group, by methods described in the literature.

The diprotected benzoic acid derivative XII is then converted to a compound of formula XIV by known technology. In one procedure XII is hydrolyzed to the corresponding acid ($Y_2 = OH$), or lithium salt, and reacted with the appropriate alkyl lithium to produce an alkyl disubstituted phenyl ketone (Y_2 = alkyl). When methyl lithium is used, the resulting acetophenone derivative is treated with a Grignard Reagent (W—Z'—MgBr). The intermediate adduct is hydrolyzed to the corresponding alcohol which is then hydrogenolyzed to replace the hydroxy group with hydrogen. This procedure is especially useful for those compounds wherein Z is alkylene.

The ether groups are deblocked by suitable means: treatment with pyridine hydrochloride (Y_1 = methyl) or catalytic hydrogenolysis (Y_1 = benzyl), or by treatment with an acid such as trifluoroacetic acid, hydrochloric, hydrobromic or sulfuric acids. Acid debenzylation is, of course, used when the group —Z—W contains sulfur.

A further method for converting compounds of formula XII to those of formula XIV comprises reaction of a ketone of formula XII (Y_2 = alkyl) with the appropriate triphenyl phosphonium bromide derivative $[(C_6H_5)_3\overset{+}{P}—Z—W]\overset{-}{Br}$ in the presence of a base (e.g., sodium hydride). The reaction proceeds via an alkene which is subsequently catalytically hydrogenated to the corresponding alkane (Z—W) and deblocked to the dihydroxy compound XIV. Of course, when —Z— is $(alk_1)_m—X—(alk_2)_n$ and Y_1 is benzyl, the catalytic hydrogenation also results in cleavage of the benzyl ethers.

Alternatively, conversion of structure XII compounds to those of structure XIV can be achieved by the sequence XII → XIII → XIV. In this sequence, the diprotected benzamide (XII, $Y_2 = NH_2$) is converted to the ketone (XIII, Z' = Z less one CH_2 group) by reaction with the appropriate Grignard reagent (BrMg—Z'—W) followed by reaction with methyl- or ethyl-magnesium halide to form the corresponding carbinol. Dehydration of the carbinol, e.g., with p-toluenesulfonic acid, affords the corresponding alkene which is then catalytically hydrogenated (Pd/C) to the alkane (XIV). The ether groups are deblocked (converted to hydroxy) as described above.

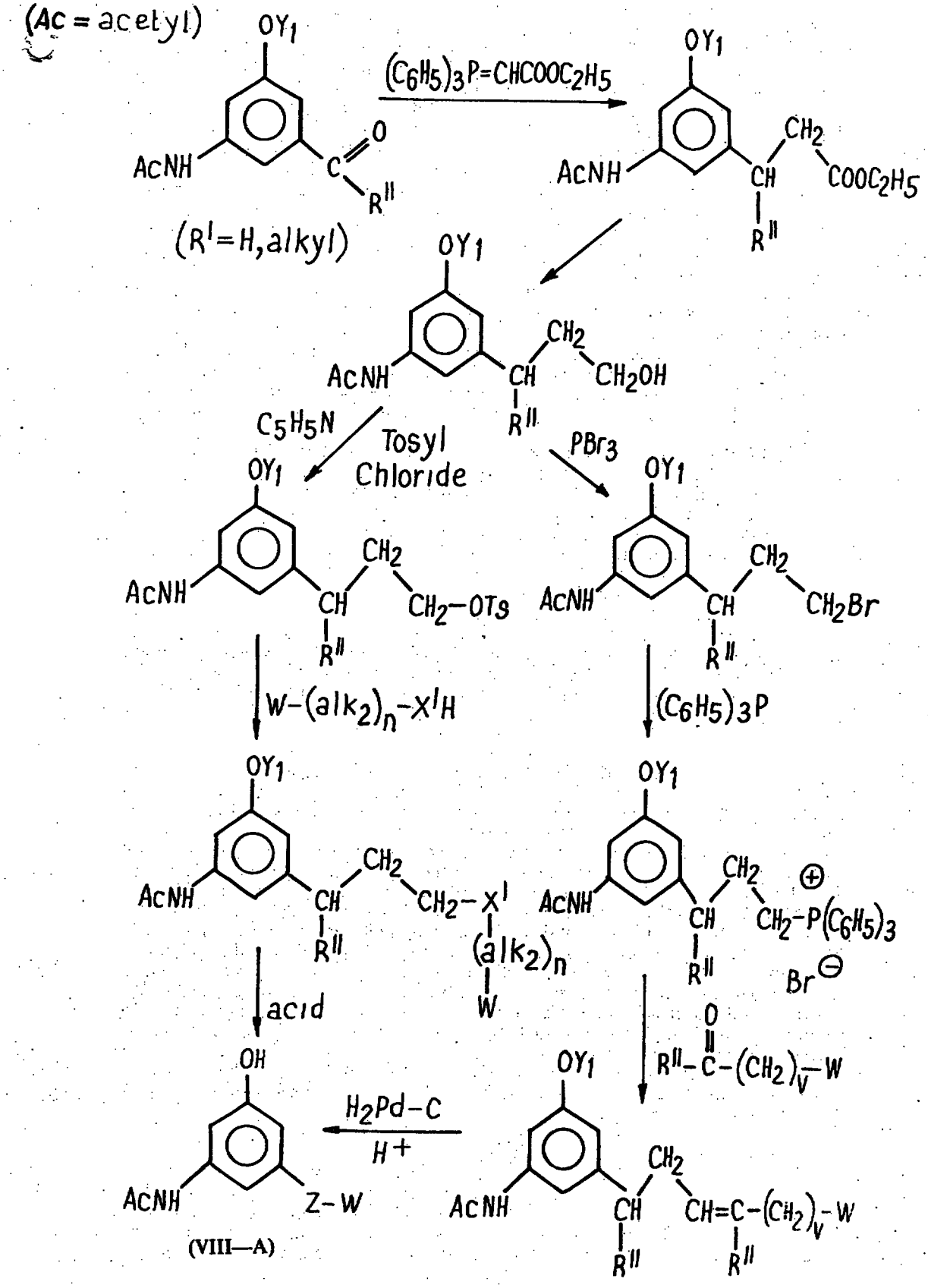
When Z is alkylene, Y_1 is desirably alkyl having from one to four carbon atoms or benzyl. The function of group Y_1 is to protect the hydroxy groups during subsequent reactions. It is its ability to perform a specific function; i.e., protection of the hydroxy groups, rather than its structure which is important. The selection and identification of appropriate protecting groups can easily and readily be made by one skilled in the art. The suitability and effectiveness of a group as a hydroxy protecting group are determined by employing such a group in the above-illustrated reaction sequence. It should, therefore, be a group which is easily removed to permit restoration of the hydroxy groups. Methyl is favored as a protecting alkyl group since it is easily removed by treatment with pyridine hydrochloride. The benzyl group, if used as a protecting group, is removed by catalytic hydrogenolysis or acid hydrolysis.

When Z is $—(alk_1)_m—X—(alk_2)_n—$, Y_1 is preferably benzyl or a substituted benzyl group since it can subsequently be removed without detriment to the Z group.

Formula VIII—A compounds can, alternatively, be prepared from 3-amino-5-hydroxybenzoic acids via the procedure of Flow Sheet F below.

Compounds of formula VIII—A wherein —Z—W is —alkylene—W or $—(alk_1)—X'—(alk_2)_n—W$ wherein (alk_1), (alk_2), W and n are as defined above and X' is O or S, are obtained by the following sequence (Flow Sheet F):

Flow Sheet F



(VIII—A)

The first step in the above sequence (the Wittig reaction) provides opportunity, by choice of appropriate reactants, to produce compounds having straight or branched alkylene groups. The amino group is protected by acetylation according to standard procedures. In the given illustration, the value of R″ as methyl or ethyl permits formation of a compound having alkyl substitution on the carbon atom (α) adjacent to the phenyl group. Substitution of a methyl or ethyl group at other sites, e.g., the β-carbon atoms of the alkylene group, is achieved by choice of the appropriate carboalkoxy alkylidene triphenylphosphorane, e.g. $(C_6H_5)_3P=C(R'')—COOC_2H_5$. The unsaturated ester thus produced is reduced to the corresponding saturated alcohol by reaction with lithium aluminum hydride. The presence of a small amount of aluminum chloride sometimes accelerates this reaction. Alternatively, when Y_1 is other than benzyl (e.g. methyl), the alcohol is produced by catalytic reduction of the unsaturated ester using palladium-carbon, followed by treatment of the saturated ester thus produced with lithium aluminum hydride. Conversion of the alcohol to the corresponding tosylate or mesylate followed by alkylation of the tosylate or mesylate with an alkali metal salt of the appropriate $HX'—(alk_2)_n—W$ reactant, and finally removal of the protecting groups (Y_1) affords the desired compound VIII—A. When X′ is sulfur, the protecting group Y_1 is methyl.

A variation of the above sequence comprises bromination of the alcohol rather than converting it to a tosylate or mesylate. Phosphorous tribromide is a convenient brominating agent. The bromo derivative is then reacted with the appropriate $HX'—(alk_2)_n—W$ in the presence of a suitable base (Williamson reaction).

The bromo compounds also serve as valuable intermediates for increasing the chain length of the alkylene moiety in the above sequence to give compounds wherein Z is —alkylene—W. The process comprises trating the bromo derivative with triphenyl phosphine to produce the corresponding triphenylphosphonium bromide. Reaction of the triphenylphosphonium bromide with the appropriate aldehyde or ketone in the presence of a base such as sodium hydride or n-butyl lithium affords an unsaturated derivative which is then catalytically hydrogenated to the corresponding saturated compound.

In this variation, the value of the protecting group (Y_1) selected depends upon the particular sequence followed. When the vertical sequence on the right is used, benzyl is the preferred protecting group by reason of the catalytic hydrogenation step. Methyl is the preferred protecting group when the left vertical sequence is followed, since it is conveniently removed by treatment with acid as described herein.

Example 1.

Ethyl dl-*3-(3,5-Dimethoxyanilino)butyrate.*

A mixture of 3,5-dimethoxyaniline (95.7 g., 0.624 mole), ethyl acetoacetate (87.2 ml., 0.670 mole), benzene (535 ml.) and glacial acetic acid (3.3 ml.) is refluxed for 15 hours under an atmosphere of nitrogen and water collected by means of a Dean-Stark trap. The reaction mixture is cooled to room temperature, decolorized with activated charcoal, filtered, and then concentrated under reduced pressure to give the product, ethyl 3-[3,4-dimethoxy)anilino]-2-butenoate, as an oil (168.7 g.).

A mixture of ethyl 3-(3,5-dimethoxyanilino)-2-butenoate (5.0 g., 18.7 mmole) in glacial acetic acid (42 ml.) and platinum oxide (250 mg.) is hydrogenated in a Parr shaker at 50 p.s.i. for 1.5 hours. The reaction mixture is filtered through filter-aid, benzene (50 ml.) added and the solution concentrated under reduced pressure to an oil. The oil is taken up in chloroform, the solution washed successively with saturated sodium bicarbonate solution (2 x 50 ml.) and saturated sodium chloride solution. It is then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the product as an oil (5.1 g.).

Repetition of the above procedure but using 168.7 g. of ethyl 3-(3,5-dimethoxyanilino)-2-butenoate, glacial acetic acid (320 ml.) and platinum oxide (2.15 g.) gives 160.8 g. of product.

Example 2.

Ethyl dl-*3-(3,5-Dimethoxyanilino)butyrate.*

To a solution of 3,5-dimethoxyaniline hydrochloride (370 g., 1.45 mole), reagent grade methanol (4.5 l.) and ethyl acetoacetate (286.3 g., 2.64 mole) in a 12 liter round bottom, 3 neck flask fitted with mechanical stirrer and reflux condenser is added sodium cyanoborohydride (54 g., 0.73 mole) in one portion. After the

refluxing subsides (10 minutes) the mixture is heated on a steam bath for an additional 20 minutes. To the cooled reaction mixture is added additional sodium cyanoborohydride (5.4 g., 0.07 mole) and ethyl acetoacetate (28.6 g., 0.26 mole) and the mixture refluxed for 30 minutes. This latter process is repeated once more.

The reaction mixture is isolated in portions by pouring ca. 500 ml. onto 1 liter of ice-water/500 ml. methylene chloride, separating the layers and backwashing the aqueous phase with additional methylene chloride (100 ml.). (This process is repeated using 500 ml. portions until the entire reaction mixture is worked up).

The methylene chloride layers are combined and dried ($MgSO_4$), decolorized with charcoal, filtered and evaporated to yield a yellow colored oil.

The excess ethyl acetoacetate is distilled (at 130°C. oil bath temperature and 1—5 mm. pressure) leaving the crude ethyl 3-(3,5-dimethoxyanilino)butyrate (an amber colored viscous oil): 376 g. (72% yield) which is used without further purification.

It has the following spectral characteristics:

^1H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 5.82—6.0 (m,3H,aromatic), 4.20 (q,2H, ester methylene), 3.80—4.00 (m,2H,—NH and —CH—CH_3), 3.78 (s, 6H, —OCH_3), 2.40—2.55 (m,2H,—CH_2COOEt), 1.78 (d,3H,methyl) and 1.29 (t,3H, methyl).

Example 3.

dl-*Ethyl 3-(3,5-Dimethoxyanilino)hexanoate.*

Following the procedure of Example 2, condensation of 3,5-dimethoxyaniline hydrochloride and ethyl butyrylacetate gives ethyl *d,l*-3-(3,5-dimethoxyanilino)-hexanoate. It is converted to the hydrochloride salt by addition of hydrogen chloride to a methylene chloride solution thereof; m.p. 127°—129.5°C. Recrystallization from cyclohexane/benzene (5:1) gives the analytical sample, m.p. 126°—128.5°C.

Analysis: Calc'd for $C_{16}H_{25}O_4N{\cdot}HCl$: C, 57.91; H, 7.90; N, 4.22%
Found: C, 57.89; H, 7.74; N, 4.40%

m/e — 295 (m^+)

^1H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 10.76—11.48 (b, variable, 2H, NH_2+), 6.77 (d, J=2Hz, 2H, meta H's), 6.49, 6.45 (d of d, J=2Hz, 1H, meta H), 4.08 (q, 2H, OCH_2), 3.77 (s, 6H, $[OCH_3]_2$), ca. 3.5—4.8 (m, 1H, CH—N), 2.90 (t, 2H, CH_2—C=O), ca. 1.4—2.2 (m, 4H, $[CH_2]_2$), 1.21 (t, 3H, O—C—CH_3), 0.84 (t, 3H, —C—CH_3).

Example 4.

d,l-*Ethyl 3-[(3,5-Dimethoxy-N-ethoxycarbonyl)anilino]butyrate.*

Method A —

Ethyl chloroformate (71.4 ml. 0.75 mole) is added dropwise over a 45 minute period to a mixture of ethyl 3-(3,5-dimethoxyanilino)butyrate (159.8 g., 0.598 mole), methylene chloride (100 ml.), and pyridine (100 ml., 1.24 moles) at 0°C. under a nitrogen atmosphere. The mixture is stirred for 40 minutes following addition of the ethyl chloroformate and is then poured into a mixture of chloroform (750 ml.) and ice-water (500 ml.). The chloroform layer is separated, washed successively with 10% hydrochloric acid (3 × 500 ml.), saturated aqueous sodium bicarbonate (1 × 300 ml.) and saturated aqueous sodium chloride (1 × 400 ml.) and then dried ($MgSO_4$). It is then decolorized with activated charcoal and concentrated under reduced pressure to an oil (215 g.). The product is used as is.

Method B —

Under a positive nitrogen atmosphere a mixture of ethyl 3-(3,5-dimethoxyanilino)butyrate (376 g., 1.4 mole), methylene chloride (1.4 liters) and anhydrous potassium carbonate (388.8 g., 2.81 mole) is stirred and cooled in an ice bath to 0° → 5°C. Ethyl chloroformate (153 g., 1.41 mole) is added in one portion. The mixture is allowed to warm to room temperature over a period of one hour, ethyl chloroformate (153 g., 1.41 mole) is added once more and the mixture is refluxed on a steam bath for one hour. It is then allowed to cool to room temperature and the potassium carbonate removed by filtration. The red colored filtrate is washed successively with water (2 × 1000 ml.), brine (1 × 500 ml.), dried ($MgSO_4$), and then

decolorized and evaporated under reduced pressure to afford 439 g. of crude product which is used without further purification.

^{1}H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 6.2—6.42 (m, 3H, aromatic), 4.65 (sextet, 1H, —N—CH—, CH_3), 4.10—4.15 (2 quartets, 4H, ester methylenes), 3.70 (s, 6H, —OCH_3), 2.30—2.60 (m, 2H, —CH_2COOEt), 1.00—1.40 (m, 9H, 3 methyl).

Example 5.

d,l-3-[(3,5-Dimethoxy-N-ethoxycarbonyl)anilino]butyric Acid.

Method A —

Ethyl 3-[(3,5-dimethoxy-N-ethoxycarbonyl)anilino]butyrate (202 g., 0.595 mole), aqueous sodium hydroxide (595 ml. of 1N) and ethanol (595 ml.) are combined and stirred at room temperature overnight. The reaction mixture is concentrated to about 600 ml. volume under reduced pressure, the concentrate diluted with water to 1200 ml. volume and extracted with ethyl acetate (3 x 750 ml.). The aqueous layer is then acidified with 10% hydrochloric acid to pH 2 and extracted again with ethyl acetate (3 x 750 ml.). These latter extracts are combined, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title product as an oil (163.5 g., 88.2%).

Method B —

A 5 liter 3 neck, round bottom flask equipped with mechanical stirrer and reflux condensor is charged with a solution of ethyl 3-[(3,5-dimethoxy-N-ethoxycarbonyl)anilino]-butyrate (439 g., 1.41 moles) in ethanol (2 liters). Sodium hydroxide (2 liters of 1*N*) is added and the mixture refluxed on a steam bath for 3 hours. The reaction mixture is poured onto 5 liters of ice-water and extracted in one liter portions with diethyl ether (500 ml./portion). The aqueous layer is cooled by adding ca. one liter of ice and then acidified with concentrated hydrochloric acid (1.75 ml., 2.1 moles). It is extracted in portions of one liter with methylene chloride (250 ml./portion). The methylene chloride layers are combined and dried over magnesium sulfate, decolorized with charcoal and evaporated to dryness to yield a viscous yellow oil. Crystallization from ether/cyclohexane (1:2) affords 224 g. (55.3%) of crystalline product, m.p. 78°—80°C. This material is used without further purifications in the following step.

^{1}H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 6.24—6.53 (m, 3H, aromatic), 4.65 (sextet, 1H, —$N(COOC_2H_5)CH(CH_3)CH_2COOC_2H_5$), 4.10 (quartet, 2H, ester methylene), 3.78 (s, 6H, —OCH_3), 2.40—2.60 (m, 2H, —CH_2COOH), 1.18 (t), 1.28 (d, 6H,methyl), 10.8 (bs, variable, 1H, COOH).

MS (mol.ion) m/e — 311.

An analytical sample, obtained by recrystallization from ethyl acetate/hexane (1:5), melted at 89°—91°C.

Analysis: Calc'd for $C_{15}H_{21}O_6N$: C, 57.86; H, 6.80; N, 4.50%
Found: C, 58.08; H, 6.65; N, 4.46%

Example 6.

d- *and* l-*3[(3,5-Dimethoxy-4-N-ethoxycarbonyl)anilino]butyric Acids.*

A mixture of *d,l*-3-[(3,5-dimethoxy-N-ethoxycarbonyl)anilino]butyric acid (136.6 g., 0.44 mole) and *l*-ephedrine (72.5 g., 0.44 mole) is dissolved in methylene chloride (500 ml.). The methylene chloride is then removed *in vacuo* to yield the l-ephedrine salt of *d,l*-3-[(3,5-dimethoxy-N-ethoxycarbonyl)anilino]butyric acid as an oil, $[\alpha]_D^{25} = -20.0$ (c=1.0, $CHCl_3$). Addition of ether (1500 ml.) causes crystallization of a white solid which is separated by filtration and dried (102 g.), m.p. 114°—116°C. Recrystallization from ethyl acetate/hexane (1:1) affords 71.1 g. (34%) of the *l*-ephedrine salt of *l*-3-[(3,5-dimethoxy-N-ethoxycarbonyl)anilino]-butyric acid; m.p. 126°—127°C.

Analysis: Calc'd for $C_{25}H_{38}O_7N_2$: C, 63.00; H, 7.61; N, 5.88%
Found: C, 62.87; H, 7.64; N, 5.88%

$[\alpha]_D^{25} = -43.5°$ (c=1.0, $CHCl_3$).

The *l*-ephedrine salt of the *l*-isomer is stirred in a mixture of ethyl acetate (1000 ml.) and 10% hydrochloric acid (400 ml.) for ten minutes. The organic phase is separated, washed with 10% hydrochloric acid (2 x 400 ml.), dried and concentrated under reduced pressure to an oil. Crystallization of the oil from ethyl

acetate/hexane (400 ml. of 1:1) affords 34.6 g. of *l*-3-[(3,5-dimethoxy-N-ethoxycarbonyl)anilino]butyric acid, m.p. 96°—97°C.

Analysis: Calc'd for $C_{15}H_{21}O_6N$: C, 57.86; H, 6.80; N, 4.50%
Found: C, 57.90; H, 6.66; N, 4.45%

$[\alpha]_D^{25} = -25.4°$ (c=1.0, $CHCl_3$).

The mother liquor remaining from recrystallization of the *l*-ephedrine salt of the *l*-isomer is treated with hydrochloric acid as described above to give crude *d*-3-[(3,5-dimethoxy-N-ethoxycarbonyl)anilino]butyric acid. Treatment of the crude acid with *d*-ephedrine affords, after crystallization from ether, the *d*-ephedrine salt of the *d*-isomer, m.p. 124°—125°C.

Analysis: Calc'd for $C_{25}H_{36}O_7N_2$: C, 63.00; H, 7.61; N, 5.88%
Found: C, 62.82; H, 7.47; N, 5.97%

$[\alpha]_D^{25} = +44.0$ (c=1.0, $CHCl_3$).

The *d*-ephedrine salt is converted to *d*-3-[(3,5-dimethoxy-N-ethoxycarbonyl)-anilino]butyric acid in the same manner as described above for conversion of the *l*-ephedrine salt to the free acid. M.p. 96°—97°C. after recrystallization from ethyl acetate/hexane (3:5).

Analysis: Calc'd for $C_{15}H_{21}O_6N$: C, 57.86; H, 6.80; N, 4.50%
Found: C, 57.95; H, 6.57; N, 4.35%

$[\alpha]_D^{25} = +25.3°$ (c=1.0, $CHCl_3$).

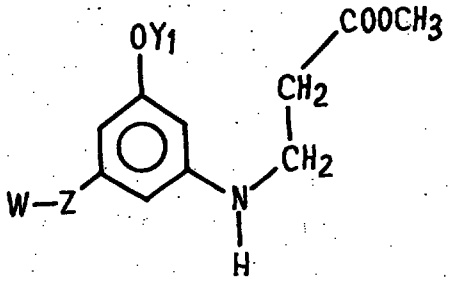
Example 7.

Methyl 3-(3,5-Dimethoxyanilino)propionate.

A mixture of 3,5-dimethoxyaniline (114.9 g., 0.75 mole), methyl acrylate (69.73 g., 0.81 mole) and glacial acetic acid (2 ml.) is refluxed for 20 hours. Reflux is discontinued and the reaction mixture is concentrated and then distilled in vacuo, to yield 106.8 g. (73.9%) of the title product, b.p. 174°—179°C. (0.7 mm.).

^1H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 5.62—5.95 (m, 3H, aromatic), 4.1 (variable, bs, 1H, —NH), 3.74 (s, 6H, $—OCH_3$), 3.68 (s, 3H, $COOCH_3$), 3.41 and 2.59 (two 2H triplets, $—NCH_2CH_2CO_2$).

Repetition of this procedure but using the appropriate aniline reactant in place of 3,5-dimethoxyaniline affords the following compounds.



Y_1	Z—W
C_2H_5	OC_2H_5
C_7H_7	OC_7H_7
C_7H_7	SCH_3
CH_3	SCH_3
C_2H_5	SCH_3

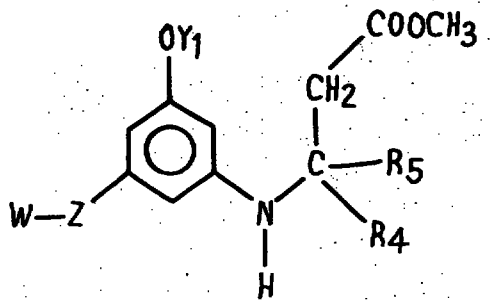
Example 8.

Methyl 3-(3,5-Dimethoxyanilino)alkanoates.

The procedure of Example 7 is repeated but using the appropriate ester $R_4R_5C=CH—COOCH_3$ in place of methyl acrylate and the appropriate protected aniline reactant to give the following compounds.

When R_5 is hydrogen, the same products are obtained by the procedure of

Examples 1 and 2 but using methyl acetoacetate and methyl propionylacetate in place of ethyl acetoacetate and the appropriate protected aniline reactant.



Y_1	Z—W	R_4	R_5
CH_3	OCH_3	CH_3	H
CH_3	OCH_3	C_2H_5	H
C_2H_5	OC_2H_5	CH_3	CH_3
CH_3	SCH_3	CH_3	H
CH_3	SCH_3	C_2H_5	H
C_7H_7	SCH_3	C_2H_5	H
C_2H_5	OC_2H_5	C_2H_5	CH_3
C_7H_7	OC_7H_7	CH_3	H
C_7H_7	OC_7H_7	C_2H_5	H
C_2H_5	SCH_3	CH_3	CH_3
C_7H_7	SCH_3	CH_3	H
CH_3	OCH_3	C_2H_5	C_2H_5
CH_3	SCH_3	C_2H_5	CH_3
CH_3	OCH_3	CH_3	CH_3
CH_3	OCH_3	$n\text{-}C_3H_7$	H
CH_3	OCH_3	$n\text{-}C_4H_9$	H
CH_3	OCH_3	$n\text{-}C_6H_{13}$	H
CH_3	SCH_3	$n\text{-}C_3H_7$	H
CH_3	SCH_3	$n\text{-}C_5H_{11}$	CH_3
C_7H_7	OC_7H_7	$i\text{-}C_3H_7$	H
CH_3	OCH_3	$n\text{-}C_4H_9$	CH_3
CH_3	OC_2H_5	$n\text{-}C_6H_{13}$	CH_3
CH_3	OCH_3	$CH_2C_6H_5$	H
CH_3	OCH_3	$CH_2C_6H_5$	CH_3

Y_1	Z—W	R_4	R_5
CH_3	OCH_3	$(CH_2)_4C_6H_5$	CH_3
CH_3	SCH_3	$CH_2C_6H_5$	CH_3
CH_3	OCH_3	$(CH_2)_3C_6H_5$	CH_3
CH_3	SCH_3	$(CH_2)_2C_6H_5$	C_2H_5
CH_3	SCH_3	$CH_2C_6H_5$	H
C_2H_5	OC_2H_5	C_2H_5	C_2H_5
C_7H_7	SCH_3	$(CH_2)_4C_6H_5$	C_2H_5
C_7H_7	OC_7H_7	CH_3	CH_3
C_2H_5	OC_2H_5	$(CH_2)_2C_6H_5$	CH_3

Example 9.

d,l-*Methyl 3-{[3-hydroxy-5-(5-phenyl-2-pentyl)]anilino}propionate.*

A mixture of 3-hydroxy-5-(5-phenyl-2-pentyl)-aniline (1.0 g.), methyl acrylate (345 mg.), and acetic acid (0.1 ml.) is heated at 106°—110°C. overnight. The cooled residue is dissolved in 100 ml. ethyl acetate and washed twice with 100 ml. of saturated sodium bicarbonate solution. The organic phase is then dried ($MgSO_4$) and evaporated to a crude residue which is chromatographed on 130 g. of silica gel using benzene-ether (2:1) as the eluant. After elution of less polar impurities, 540 mg. (40%), *d,l*-methyl 3-{[3-hydroxy-5-(5-phenyl-2-pentyl)]anilino}propionate is collected. It has the following spectral characteristics:

^1H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 7.14 (s, 5H, aromatic), 5.83—6.13 (m, 3H, aromatic), 3.66 (s, 3H, $—COOCH_3$), 3.37 (t, 2H, $—NCH_2$), 2.16—2.78 (m, 5H, $—CH_2COO$ and benzylic), 1.28—1.69 (m, 4H, $—(CH_2)_2—$), 1.11 (d, 3H, $>—CH_3$), 4.4—5.2 and 1.28—2.78 (variable, 1H, NH, OH).

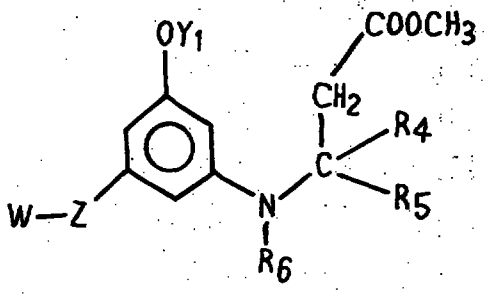
m/e — 341 (m^+).

Example 10.

Methyl 3[(3,5-Dimethoxy-N-ethoxycarbonyl)anilino]propionate.

Ethyl chloroformate (2.0 g., 8.4 mmole) is added dropwise over a 10 minute period to a mixture of methyl 3-(3,5-dimethoxyanilino)propionate (1.0 ml., 10.5 mmole), methylene chloride (5 ml.) and pyridine (5 ml.) at 0°C. under a nitrogen atmosphere. The mixture is stirred at 0°C. for 20 minutes following addition of the ethyl chloroformate and then at room temperature for an additional 20 minutes, and is then poured into a mixture of methylene chloride (75 ml.) and ice-water (50 ml.). The methylene chloride layer is separated, washed successively with 10% hydrochloric acid (2 × 50 ml.), saturated aqueous sodium bicarbonate (1 × 30 ml.) and saturated aqueous sodium chloride (1 × 40 ml.) and dried ($MgSO_4$). It is then decolorized with activated charcoal and concentrated under reduced pressure to an oil (2.72 g.). The product is used as is.

Similarly, *d,l*-methyl-3-[3-hydroxy-5-(5-phenyl-2-pentyl)anilino]propionate is converted to *d,l*-methyl-3-{[3-hydroxy-5-(5-phenyl-2-pentyl)-N-ethoxycarbonyl]-anilino}propionate and the following compounds are prepared from compounds of Examples 7 and 8 by reaction with the appropriate alkyl chloroformate or other reactant of formula R_6 Br where R_6 is other than hydrogen:



Y_1	Z—W	R_4	R_6	R_5
CH_3	OCH_3	H	COO-n-C_4H_9	H
C_2H_5	OC_2H_5	H	$CH_2COOC_2H_5$	H
C_7H_7	OC_7H_7	H	$COOCH_3$	H
C_7H_7	SCH_3	H	$COOC_2H_5$	H
CH_3	SCH_3	H	COO-n-C_3H_7	H
C_2H_5	SCH_3	H	$(CH_2)_2COOCH_3$	H
CH_3	OCH_3	CH_3	$CH_2COOC_2H_5$	H
CH_3	OCH_3	C_2H_5	$COOCH_3$	H
C_2H_5	SCH_3	CH_3	$COOCH_3$	H
CH_3	SCH_3	CH_3	$COOC_2H_5$	H
C_2H_5	OC_2H_5	C_2H_5	CH_2COO-n-C_4H_9	H
C_7H_7	OC_2H_5	C_2H_5	$COOC_2H_5$	H
C_7H_7	OC_7H_7	CH_3	$COOCH_3$	H
C_7H_7	SCH_3	C_2H_5	$COOC_2H_5$	H
C_7H_7	OC_7H_7	C_2H_5	$COOCH_3$	H
C_2H_5	SCH_3	CH_3	COO-i-C_3H_7	H
C_7H_7	SCH_3	CH_3	$(CH_2)_3COOC_2H_5$	H
CH_3	OCH_3	H	$COOC_7H_7$	H
CH_3	OCH_3	CH_3	$COOC_7H_7$	H
CH_3	OCH_3	CH_3	CH_3	H
CH_3	OCH_3	CH_3	C_2H_5	H
CH_3	OCH_3	CH_3	n-C_4H_9	H
C_2H_5	SCH_3	H	i-C_3H_7	H
C_2H_5	OCH_3	CH_3	$CH_2C_6H_5$	H
CH_3	OC_2H_5	CH_3	$(CH_2)_2C_6H_5$	H

Y_1	Z—W	R^4	R_6	R_5
C_2H_5	OCH_3	CH_3	$(CH_2)_4C_6H_5$	H
C_2H_5	SCH_3	H	CH_3	H
CH_3	OCH_3	C_2H_5	$CH_2C_6H_5$	H
CH_3	OCH_3	C_2H_5	CH_3	H
CH_3	SCH_3	C_2H_5	$(CH_2)_3C_6H_5$	H
C_2H_5	OCH_3	CH_3	$COOC_2H_5$	CH_3
C_2H_5	OCH_3	CH_3	$COOCH_3$	C_2H_5
CH_3	OCH_3	C_2H_5	$COOC_2H_5$	C_2H_5
C_2H_5	SCH_3	CH_3	$COOC_2H_5$	CH_3
CH_3	OC_2H_5	CH_3	CH_3	CH_3
CH_3	SCH_3	C_2H_5	$COOC_2H_5$	CH_3
CH_3	OCH_3	CH_3	$COOCH_2C(CH_3)_3$	CH_3
CH_3	OCH_3	CH_3	CH_2COOCH_3	H
CH_3	OCH_3	CH_3	$(CH_2)_4COOCH_3$	H
CH_3	OCH_3	CH_3	$n\text{-}C_6H_{13}$	H
CH_3	OCH_3	$n\text{-}C_3H_7$	$COOCH_3$	H
CH_3	OCH_3	$n\text{-}C_4H_9$	$COOCH_3$	H
CH_3	OCH_3	$n\text{-}C_6H_{13}$	$COOCH_3$	H
CH_3	OC_7H_7	$n\text{-}C_4H_9$	CH_3	CH_3
CH_3	SCH_3	$n\text{-}C_5H_{11}$	$CH_2C_6H_5$	CH_3
CH_3	OC_7H_7	$CH_2C_6H_5$	$(CH_2)_4C_6H_5$	CH_3
C_2H_5	OC_2H_5	$(CH_2)_2C_6H_5$	C_2H_5	CH_3
C_7H_7	SCH_3	$(CH_2)_4C_6H_5$	$n\text{-}C_5H_{11}$	C_2H_5
CH_3	OCH_3	$(CH_2)_4C_6H_5$	$COOC_2H_5$	CH_3
CH_3	OCH_3	$CH_2C_6H_5$	CH_3	CH_3
CH_3	OCH_3	CH_3	$COCH_3$	CH_3
CH_3	SCH_3	$(CH_2)_2C_6H_5$	CHO	CH_3
C_7H_7	OC_7H_7	CH_3	COC_5H_{11}	CH_3
CH_3	OCH_3	CH_3	$COCH_2C_6H_5$	CH_3
CH_3	OCH_3	CH_3	$CO(CH_2)_3C_6H_5$	H
CH_3	SCH_3	H	$COCH_3$	H
CH_3	SCH_3	H	$n\text{-}C_6H_{13}$	H

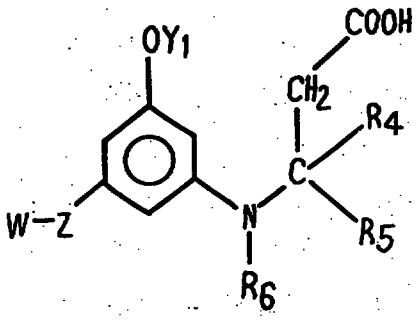
Y_1	Z—W	R^4	R_6	R_5
CH_3	SCH_3	n-C_3H_7	n-C_4H_9	H
CH_3	OCH_3	$CH_2C_6H_5$	$COOCH_3$	H
C_7H_7	OC_7H_7	i-C_3H_7	$COOC_2H_5$	H
CH_3	OC_2H_5	n-C_6H_{13}	i-C_3H_7	CH_3
CH_3	SCH_3	$CH_2C_6H_5$	$COOC_7H_7$	CH_3
CH_3	OCH_3	$(CH_2)_3C_6H_5$	$COCH_2C_6H_5$	CH_3
CH_3	SCH_3	$CH_2C_6H_5$	COO-n-C_4H_9	H
C_2H_5	OC_2H_5	CH_3	$COOC_7H_7$	CH_3

Example 11.

3-[(3,5-Dimethoxy-N-ethoxycarbonyl)anilino]propionic Acid.

Methyl 3-[(3,5-dimethoxy-N-ethoxycarbonyl)anilino]propionate (2.72 g., 8.36 mmoles), aqueous sodium hydroxide (8.4 ml. of 1N) and ethanol (8.4 ml.) are combined and stirred overnight under nitrogen at room temperature. The reaction mixture is then concentrated under reduced pressure to half-volume, diluted with water (35 ml.) and then extracted with ethyl acetate. The aqueous phase is acidified to pH 2 with 10% hydrochloric acid and extracted with methylene chloride (3 × 50 ml.). The combined extracts are washed with brine, dried ($MgSO_4$) and concentrated to give the product as an oil (2.47 g.) which is used as is.

In like manner, the remaining compounds of Example 10 are hydrolyzed to their corresponding alkanoic acids having the formula



Example 12.

1-Carbethoxy-5,7-dimethoxy-4-oxo-1,2,3,4-tetrahydroquinoline.

A mixture of 3-[(3,5-dimethoxy-N-ethoxycarbonyl)anilino]propionic acid (1.10 g., 3.7 mmole) and polyphosphoric acid (4 g.) is heated at 65°C. for 45 minutes under an atmosphere of nitrogen and is then cooled to 0°C. It is then taken up in a mixture of methylene chloride-water (200 ml. of 1:1). The organic layer is separated and the aqueous phase extracted again with methylene chloride (2 × 100 ml.). The combined extracts are washed with saturated sodium bicarbonate (3 × 100 ml.), brine (1 × 100 ml.) and then dried ($MgSO_4$). Concentration of the dried extract gives the product as an oil which crystallizes from benzene. Yield = 645 mg., m.p. 109°—111°C.

Analysis: Calc'd for $C_{14}H_{17}O_5N$: C, 60.21; H, 6.14; N, 5.02%
Found: C, 60.11; H, 6.14; N, 4.80%

Example 13.

5,7-Dihydroxy-4-oxo-1,2,3,4-tetrahydroquinoline.

A mixture of glacial acetic acid (60 ml.), 48% hydrobromic acid (60 ml.) and 1-carbethoxy-5,7-dimethoxy-4-oxo-1,2,3,4-tetrahydroquinoline (4.0 g., 14.3 mmole) is refluxed overnight and is then concentrated *in vacuo* to a dark oil. The oil is dissolved in water (50 ml.) and the aqueous solution neutralized to pH 6—7 with 1N

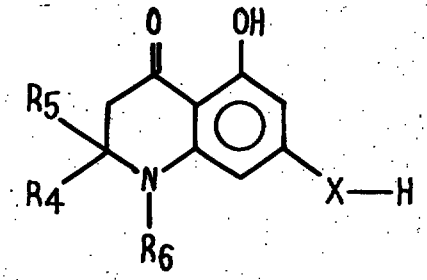
sodium hydroxide. A saturated solution of salt water (50 ml.) is added and the resulting mixture extracted with ethyl acetate (3 x 150 ml.). The extracts are combined, dried ($MgSO_4$) and concentrated under reduced pressure to an oil. The oil is taken up in benzene-ethyl acetate (1:1) and the solution charged to a silica gel column. The column is eluted with a volume of benzene equal to the volume of the column and then with benzene-ethyl acetate (250 ml. of 4:1) and benzene-ethyl acetate (250 ml. of 1:1). Fractions (75 ml.) are collected. Fractions 4—9 are combined and evaporated under reduced pressure. The oily residue is crystallized from ethanol-hexane (1:10). Yield = 1.86 g., m.p. 166°—169°C.

Further recrystallization raises the melting point to 171°—172.5°C.

m/e — 179 (m^+)

Analysis: Calc'd for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82%
Found: C, 60.25; H, 4.94; N, 7.55%

By means of the procedure of Example 12 and this procedure, 3-[3-hydroxy-5-(5-phenyl-2-pentyl)-N-ethoxycarbonyl]anilino]propionic acid is transformed to 5-hydroxy-7-(5-phenyl-2-pentyl)-4-oxo-1,2,3,4-tetrahydroquinoline, and the following compounds are prepared from compounds of Example 11:



R_6	R_4	X—H	R_5
H	C_2H_5	OH	H
H	H	SH	H
H	CH_3	SH	H
H	C_2H_5	SH	H
CH_3	H	OH	H
CH_3	CH_3	OH	H
C_2H_5	CH_3	OH	H
n-C_4H_9	CH_3	OH	H
i-C_3H_7	H	SH	H
$CH_2C_6H_5$	CH_3	OH	H
$(CH_2)_2C_6H_5$	CH_3	OH	H
$(CH_2)_4C_6H_5$	CH_3	OH	H
CH_3	H	SH	H
CH_3	C_2H_5	OH	H
$CH_2C_6H_5$	CH_3	SH	H
$(CH_2)_3C_6H_5$	C_2H_5	SH	H
C_2H_5	H	OH	H

R_6	R_4	X—H	R_5
CH_3	CH_3	SH	H
H	CH_3	OH	CH_3
H	C_2H_5	OH	C_2H_5
H	CH_3	OH	C_2H_5
$n\text{-}C_6H_{13}$	CH_3	OH	H
H	CH_3	SH	CH_3
H	C_2H_5	SH	C_2H_5
CH_2COOH	H	OH	H
CH_2COOH	C_2H_5	OH	H
CH_2COOH	CH_3	OH	H
$(CH_2)_2COOH$	H	SH	H
$(CH_2)_3COOH$	CH_3	SH	H
$(CH_2)_4COOH$	CH_3	OH	H
H	$n\text{-}C_3H_7$	OH	H
H	$n\text{-}C_4H_9$	SH	H
H	$n\text{-}C_6H_{13}$	OH	H
H	CH_3	OH	CH_3
H	$n\text{-}C_4H_9$	OH	CH_3
H	$n\text{-}C_4H_9$	OH	C_2H_5
H	$n\text{-}C_6H_{13}$	OH	CH_3
H	$CH_2C_6H_5$	OH	CH_3
H	$(CH_2)_2C_6H_5$	OH	CH_3
H	$(CH_2)_4C_6H_5$	OH	CH_3
H	$CH_2C_6H_5$	SH	CH_3
H	$(CH_2)_3C_6H_5$	SH	C_2H_5
CH_3	CH_3	OH	CH_3
$n\text{-}C_3H_7$	CH_3	OH	CH_3
$n\text{-}C_6H_{13}$	CH_3	OH	CH_3
$n\text{-}C_4H_9$	$CH_2C_6H_5$	OH	CH_3
CH_3	$n\text{-}C_4H_9$	OH	CH_3
$CH_2C_6H_5$	CH_3	OH	CH_3
$(CH_2)_4C_6H_5$	CH_3	OH	CH_3

R_6	R_4	X—H	R_5
$CH_2C_6H_5$	$(CH_2)_3C_6H_5$	OH	CH_3
CH_2COOH	CH_3	OH	CH_3
$(CH_2)_2COOH$	CH_3	OH	CH_3
$(CH_2)_4COOH$	C_2H_5	OH	CH_3
CH_3	CH_3	OH	CH_3
CH_2COOH	C_2H_5	OH	CH_3
$CH_2C_6H_5$	CH_3	SH	CH_3
$(CH_2)_3C_6H_5$	CH_3	SH	CH_3
CH_3	CH_3	SH	CH_3
CH_3	$CH_2C_6H_5$	SH	CH_3
i-C_3H_7	n-C_4H_9	SH	C_2H_5
CH_2COOH	$(CH_2)_2C_6H_5$	SH	C_2H_5
n-C_5H_{11}	CH_3	SH	CH_3
$(CH_2)_4COOH$	CH_3	SH	CH_3
$CH_2C_6H_5$	$(CH_2)_3C_6H_5$	SH	CH_3
H	n-C_6H_{13}	SH	CH_3
$CH_2C_6H_5$	C_2H_5	OH	H
n-C_4H_9	C_2H_5	OH	H
$CH_2C_6H_5$	H	OH	H
$(CH_2)_2COOH$	CH_3	SH	H
$(CH_2)_4COOH$	H	OH	H
H	$CH_2C_6H_5$	SH	H
i-C_3H_7	CH_3	SH	CH_3
$(CH_2)_3C_6H_5$	CH_3	SH	CH_3

Example 14:

d,l-1-Carbethoxy-5,7-dimethoxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline.

A solution of 3-[(3,5-dimethoxy-N-ethoxycarbonyl)anilino]butyric acid (4.0 g., 12.8 mmole) in chloroform (2 ml.) is added dropwise with stirring to polyphosphoric acid (5.0 g.) heated to 60°C. on a steam bath. The reaction mixture is held at 60°—65°C. for two hours and is then poured into a mixture of ice (100 g.) and ethyl acetate (100 ml.). The aqueous layer is further extracted with ethyl acetate (2 x 100 ml.) and the combined organic extracts washed successively with saturated sodium bicarbonate solution (3 x 100 ml.), brine (1 x 100 ml.), and then dried over anhydrous magnesium sulfate. Concentration of the dried extract under reduced pressure gives 2.6 g. of crude product.

Purification is accomplished by column chromatography of a benzene solution of the crude product (2.5 g.) on silica gel (95 g.). The column is eluted with a volume of benzene equal to one-half the volume of the column, followed by

benzene/ethyl acetate (1:1). Fractions (40 ml.) are collected. Fractions 9—18 are combined and evaporated *in vacuo* to give 1.55 g. of product which is purified further by recrystallization from petroleum ether — 1.33 g., m.p. 92.5°—94°C.

Recrystallization of this product from hot ethyl acetate/hexane (1:1) affords an analytical sample; m.p. 94°—95°C.

Analysis: Calc'd for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.53; N, 4.78%
Found: C, 61.54; H, 6.55; N, 4.94%

m/e — 293 (m^+)

IR (KBr) — 5.85, 5.95 μ (>=O)

Example 15.

d,l-*5,7-Dihydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline.*

Method A —

A mixture of glacial acetic acid (240 ml.), 48% hydrobromic acid (240 ml.) and l-carbethoxy-5,7-dimethoxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline (16.0 g., 55 mmole) is refluxed overnight and is then concentrated *in vacuo* to a dark oil. The oil is dissolved in water (200 ml.) and the aqueous solution neutralized to pH 6—7 with 1N sodium hydroxide. A saturated solution of salt water (200 ml.) is added and the resulting mixture extracted with ethyl acetate (3 x 500 ml.). The extracts are combined, dried ($MgSO_4$) and concentrated under reduced pressure to a dark oil (12.8 g.). Hexane-ethyl acetate (10:1) is added to the oil and the resulting crystals recovered by filtration (3.8 g.); m.p. 158—165°C. Trituration of the crystals in ethyl acetate gives 1.65 g. of product; m.p. 165°—168°C.

Additional material separates from the mother liquors on standing (2.9 g.) m.p. 168°—170°C. Column chromatography of the filtrate on silica gel using benzene-ether (1:1) as solvent gives an additional 4.6 g. of product, m.p. 167°—169°C.

Further purification is achieved by recrystallizing the product from ethyl acetate; m.p. 173°—174°C.

Analysis: Calc'd for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25%
Found: C, 62.00; H, 5.83; N, 7.14%

m/e — 193 (m^+)

Method B —

A mixture of *d,l*-3-[(3,5-dimethoxy-N-ethoxycarbonyl)anilino]butyric acid (100 g., 0.32 mole) and 48% hydrobromic acid (500 ml.)/glacial acetic acid (300 ml.) is heated in an oil bath at 110°C. for 2 hours. The oil-bath temperature is then increased to 145°C. and heating is continued for an additional 2 hours. During this last heating period an azeotropic mixture distills (boiling point 42° → 110°C. ~200—300 ml.) and the deep-red homogeneous solution is allowed to cool to room temperature. The mixture is poured onto ice-water (3 liters) and ether (2 liters), the layers are separated and the aqueous solution is washed with ether (2 x 1000 ml.). The ether layers are combined and washed successively with water (2 x 1000 ml.), brine (1 x 500 ml.), saturated $NaHCO_3$ solution (4 x 250 ml.) and brine (1 x 500 ml.) and then dried ($MgSO_4$). Decolorization with charcoal and evaporation of the ether affords a yellow foam which is crystallized from ca. 300 ml. methylene chloride to give 31.3 g. (50.4%) of pure 5,7-dihydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline. Additional product can be isolated from the mother liquor by silica gel chromatography.

^{1}H NMR (60 MHz) δ^{TMS} (100 mg. sample/0.3 ml. $CDCl_3$/0.2 ml. CD_3SOCD_3) (ppm): 12.40 (s,1H,C_5—OH), 5.72 (d,2H,meta H), 5.38—5.60 (bs,1H,C_7—OH), 3.50—4.00 (m,1H,C2H), 2.38—2.60 (m,2H,C_3—H_2), 1.12 (d,3H,methyl).

m/e — 193 (m^+)

Analysis: Calc'd for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25%
Found: C, 62.01; H, 5.85; N, 7.02%

Similarly, methyl *d,l*-3-[[3-hydroxy-5-(5-phenyl-2-pentyl)]anilino]propionate is converted to *d,l*-5-hydroxy-7-(5-phenyl-2-pentyl)-4-oxo-1,2,3,4-tetrahydroquinoline which is purified by column chromatography using silica gel and benzene/ether (5:1) as eluant.

m/e — 309 (m^+)

^{1}H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 12.22 (s, 1H, 50H), 7.14 (s, 5H, C_6H_5), 6.04 (d, J=2.5Hz, 1H meta H), 5.87 (d, J=2.5Hz, 1H meta H), 4.19—4.60 (b, 1H, NH), 3.48 (t, 2H, CH_2N), 2.18—2.89 (m, 5H, ArCH, $ArCH_2$, CH_2—C=O),

1.38—1.86 (m, 4H, —$[CH_2]_2$—), 1.13 (d, 3H, CH_3).

and ethyl *d,l*-3-(3,5-dimethoxyanilino)hexanoate hydrochloride is converted to *d,l*-5,7-dihydroxy-2-propyl-4-oxo-1,2,3,4-tetrahydroquinoline; m.p. 117°—119°C. (from methylene chloride).

m/e — 221 (m^+), 135 (base peak, m^+ — propyl).

and *l*-3-[(3,5-dimethoxy-(N-ethoxy carbonyl)anilino]butyric acid is converted to *d*-5,7-dihydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline, m.p. 167°—168°C. $[\alpha]_D^{25}$ = +167.8° (c=1.0, CH_3OH).

m/e — 193 (m^+)

Analysis: Calc'd for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25%
Found: C, 61.87; H, 5.62; N, 6.96%

and *d*-3-[3,5-dimethoxy-N-ethoxycarbonyl)anilino]butyric acid is converted to *l*-5,7-dihydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline; m.p. 166°—168°C. $[\alpha]_D^{25}$ = −168.5° (c=1.0, CH_3OH).

m/e — 193 (m^+)

Analysis: Calc'd for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25%
Found: C, 61.82; H, 5.83; N, 7.22%

Example 16.

d,l-*5,7-Dihydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline.*

A mixture of 3,5-dimethoxyaniline (230 g., 1.5 moles), methyl crotonate (150 g., 1.5 moles) and glacial acetic acid (90 g., 1.5 moles) is heated at reflux for 6 hours. Additional glacial acetic acid (90 g., 1.5 moles) is added and the mixture refluxed overnight. Hydrobromic acid (1000 ml. of 48% solution) and glacial acetic acid (850 ml.) are added to the reaction mixture which is heated at reflux for 4.5 hours. The title product is isolated and purified according to the procedure of Example 13. Yield = 36 g., m.p. 166°—170°C.

Repetition of this procedure but replacing methyl crotonate with methyl acrylate, methyl 3-ethyl acrylate or methyl 3,3-dimethylacrylate affords 5,7-dihydroxy-4-oxo-1,2,3,4-tetrahydroquinoline, 5,7-dihydroxy-2-ethyl-4-oxo-1,2,3,4-tetrahydroquinoline, and 5,7-dihydroxy-2,2,-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline, respectively.

Example 17.

d,l-*5,7-Dihydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline.*

A mixture of 3,5-dimethoxyaniline (4,6 g., 0.03 mole), crotonic acid (2.54 g., 0.03 mole) and pyridine hydrochloride (3.0 g., 1.26 moles) is heated at 185°—200°C. for 45 minutes. The cooled reaction mixture is suspended in water (500 ml.) (pH ~3) and the pH adjusted to 7 and the resultant mixture stirred for 10 minutes. The organic layer is separated, dried ($MgSO_4$) and concentrated to 3.2 g. of a yellow oil.

A mixture of glacial acetic acid (110 ml.), 48% hydrobromic acid (110 ml.) and the yellow oil is refluxed for one hour and is then concentrated *in vacuo* to a dark oil. The oil is dissolved in water and the aqueous solution neutralized to pH 6—7 with 1N sodium hydroxide. A saturated solution of salt water is added and the resulting mixture extracted with ethyl acetate. The extracts are combined, dried ($MgSO_4$) and concentrated under reduced pressure to a dark oil (2.8 g.). Column chromatography of the crude residue on silica gel using benzene-ether (4:1) as eluant gives an additional 510 mg. of product, m.p. 168°—170°C.

Further purification is achieved by recrystallizing the product from ethyl acetate; m.p. 173°—174°C.

Analysis: Calc'd for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25%
Found: C, 62.00; H, 5.83: N, 7.14%

m/e — 193 (m^+), 178 (m^+ — methyl, base peak).

In a similar manner, 3,3-dimethyl acrylic acid and 3,5-dimethoxyaniline gives after purification by silica gel chromatography (benzene/ether 1:1 as eluant) 5,7-dihydroxy-2,2-dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline as a yellow oil.

Analysis (MS)

Parent peak (m^+)

Calc'd for $C_{11}H_{13}O_3N$: 207.0895
Found: 207.0895

Base peak (m^+ — 15)

Calc'd for $C_{10}H_{10}O_3N$: 192.0661
Found: 192.0655

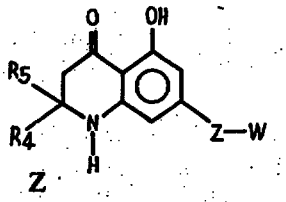
Similarly, styryl acetic acid and 3,5-dimethoxyaniline are condensed to yield *d,l*-5,7-dihydroxy-2-benzyl-4-oxo-1,2,3,4-tetrahydroquinoline as an oil after purification using benzene/ether (3:1) as eluant.

m/e = 269 (m^+) and 178 (m^+-benzyl, base peak)

NMR ($CDCl_3$) δ (ppm): 8.76 (s, 1H, 5—O*H*), 7.18—7.6 (m, 5H, C_6H_5), 5.84 (d, J=3Hz, 1H) and 5.62 (d, J=3Hz, 1H) for the metal coupled aromatics, and 2.14—4.82 (4m, 7H), for the remaining protons (7—O*H*, C*H*—N, CH_2—C=O, —CH_2—C_6H_5 and N—*H*).

Example 18.

Following the procedures of Examples 9—15, the compounds tabulated below are prepared from appropriate 3-hydroxy-5-(Z—W)anilines and appropriate esters of the formula R_4R_5C=CH—$COOCH_3$ wherein each of R_4,R_5 is hydrogen, methyl or ethyl.



R_5	R_4	Z	W
H	H	$CH(CH_3)(CH_2)_3$	C_6H_5
H	CH_3	$CH(CH_3)(CH_2)_3$	C_6H_5
H	C_2H_5	$CH(CH_3)(CH_2)_3$	C_6H_5
H	CH_3	$CH(CH_3)(CH_2)_4$	C_6H_5
H	H	$CH(CH_3)(CH_2)_3$	C_6H_5
H	H	$(CH_2)_3$	C_6H_5
H	H	$(CH_2)_4$	C_6H_5
H	C_2H_5	$(CH_2)_4$	C_6H_5
H	H	$(CH_2)_2CH(C_2H_5)$	C_6H_5
H	CH_3	$CH(C_2H_5)(CH_2)_3$	C_6H_5
H	H	$C(CH_3)_2$	C_6H_5
H	CH_3	$C(CH_3)_2(CH_2)_3$	C_6H_5
H	H	$(CH_2)_6$	C_6H_5
H	CH_3	$(CH_2)_8$	C_6H_5
H	H	$CH(CH_3)(CH_2)_7$	C_6H_5
H	H	CH_2	C_6H_5
H	H	$CH(CH_3)(CH_2)_3$	4-FC_6H_4
H	CH_3	$CH(CH_3)(CH_2)_3$	4-FC_6H_4
H	H	$CH(CH_3)CH_2$	4-FC_6H_4
H	C_2H_5	$CH(CH_3)CH_2$	4-FC_6H_4
H	C_2H_5	$CH(CH_3)(CH_2)_2$	4-ClC_6H_4
H	H	$CH(CH_3)(CH_2)_2CH(CH_3)$	C_6H_5
H	CH_3	CH_2	C_6H_5
H	H	$(CH_2)_3$	C_5H_9

R_5	R_4	Z	W
CH_3	CH_3	$CH(CH_3)(CH_2)_3$	C_6H_5
H	CH_3	$CH(CH_3)CH_2$	C_5H_9
H	H	$CH(CH_3)(CH_2)_2$	C_5H_9
H	H	$CH(CH_3)(CH_2)_4$	C_5H_9
H	H	$CH(CH_3)CH_2$	C_3H_5
H	H	$CH(CH_3)CH(CH_3)$	C_6H_{11}
H	C_2H_5	$CH(CH_3)CH(CH_3)$	C_6H_{11}
H	H	$CH(CH_3)(CH_2)_5$	C_6H_{11}
H	CH_3	$CH(CH_3)(CH_2)_5$	C_6H_{11}
H	H	$(CH_2)_4$	C_3H_5
H	H	$(CH_2)_5$	C_6H_{11}
H	C_2H_5	$(CH_2)_5$	C_6H_{11}
H	H	$(CH_2)_3CH(CH_3)$	C_6H_{11}
H	CH_3	$CH(CH_3)(CH_2)_3$	C_6H_{11}
H	H	$CH(CH_3)(CH_2)_2CH(CH_3)$	C_6H_{11}
H	CH_3	$CH(CH_3)CH(CH_3)CH_2$	C_6H_{11}
H	H	$(CH_2)_3$	2-pyridyl
H	H	$(CH_2)_3$	4-pyridyl
H	H	$(CH_2)_4$	2-pyridyl
H	CH_3	$(CH_2)_4$	4-pyridyl
H	C_2H_5	$(CH_2)_4$	3-pyridyl
H	CH_3	$CH_2CH(CH_3)CH_2$	4-pyridyl
H	C_2H_5	$CH(CH_3)(CH_2)_2$	3-pyridyl
H	CH_3	$CH(CH_3)CH(C_2H_5)CH_2$	4-pyridyl
H	H	$CH(C_2H_5)(CH_2)_3$	3-pyridyl
H	H	$CH_2CH(C_2H_5)CH_2$	3-pyridyl
H	H	$CH(CH_3)(CH_2)_2$	4-piperidyl
H	CH_3	$CH(C_2H_5)(CH_2)_2$	2-piperidyl
H	CH_3	$CH(CH_3)(CH_2)_2CH(CH_3)$	4-piperidyl
H	CH_3	$CH(CH_3)(CH_2)_2$	C_7H_{13}
H	H	$CH(CH_3)(CH_2)_2$	C_7H_{13}
H	CH_3	$CH(CH_3)CH_2—O—(CH_2)_2$	C_6H_5

R_5	R_4	Z	W
H	H	$(CH_2)_4$	CH_3
H	CH_3	$CH(CH_3)CH(CH_3)(CH_2)_5$	H
H	H	$CH(CH_3)CH(CH_3)(CH_2)_5$	H
H	H	CH_2	H
H	CH_3	CH_2	CH_3
H	H	$(CH_2)_3$	CH_3
H	H	$(CH_2)_6$	CH_3
H	CH_3	$(CH_2)_6$	CH_3
H	H	$CH(CH_3)$	CH_3
H	CH_3	$(CH_2)_3$	H
H	H	$CH(CH_3)$	C_6H_{11}
H	C_2H_5	$CH(CH_3)(CH_2)_4$	CH_3
H	H	$(CH_2)_3$—O—	C_6H_5
H	CH_3	$(CH_2)_3$—O—	4-FC_6H_4
H	CH_3	$(CH_2)_3$—O—	C_6H_{11}
H	C_2H_5	$(CH_2)_3$—O—	C_4H_7
H	H	$(CH_2)_3$—O—	CH_3
H	CH_3	$(CH_2)_3$—O—	4-(4-FC_6H_4)C_6H_{10}
H	C_2H_5	$(CH_2)_3$—O—$(CH_2)_2$	4-ClC_6H_4
H	H	$(CH_2)_3$—O—$(CH_2)_2$	C_6H_5
H	CH_3	$(CH_2)_3$—O—$CH(CH_3)$	4-piperidyl
H	CH_3	$(CH_2)_3$—O—$CH(CH_3)(CH_2)_2$	C_6H_5
H	H	$(CH_2)_3$—O—$CH(CH_3)(CH_2)_2$	CH_3
H	H	$CH(C_3H_7)(CH_2)_2$—O—	C_6H_5
H	CH_3	$CH(CH_3)(CH_2)_2$—O—CH_2	CH_3
H	CH_3	$CH(CH_3)(CH_2)_2$—O—$(CH_2)_4$	C_6H_5
H	CH_3	$CH(CH_3)(CH_2)_2$—O—$CH(CH_3)$	C_7H_{13}
H	H	$CH(CH_3)(CH_2)_2$—O—CH_2CH—(C_2H_5)	CH_3
H	CH_3	$(CH_2)_4$—O—	C_6H_5
H	H	$(CH_2)_4$—O—$CH(CH_3)CH_2$	3-piperidyl
H	C_2H_5	$(CH_2)_4$—O—$(CH_2)_5$—	4-pyridyl
H	C_2H_5	$(CH_2)_4$—O—CH_2	4-FC_6H_4

R_5	R_4	Z	W
H	H	$CH(CH_3)(CH_2)_3$—O—	2-(4-FC_6H_5)C_5H_8
H	CH_3	$CH(CH_3)(CH_2)_3$—O—$(CH_2)_2$	C_6H_5
H	C_2H_5	$CH(CH_3)(CH_2)_3$—O—$(CH_2)_2$	CH_3
H	H	$CH(C_2H_5)(CH_2)_2$—O—$(CH_2)_4$	C_6H_5
H	CH_3	$CH(C_2H_5)(CH_2)_2$—O—$CH(CH_3)$	4-piperidyl
H	H	$CH(C_2H_5)(CH_2)_2$—O—$(CH_2)_2$—$CH(CH_3)$	C_7H_{13}
H	CH_3	$CH(CH_3)$—O—CH_2	C_5H_8
H	CH_3	$CH(C_2H_5)(CH_2)_2$—O—	C_3H_5
H	H	$CH(C_2H_5)(CH_2)_2$—O—	2-(4-FC_6H_{11})C_7H_{12}
H	H	$(CH_2)_3$—S—	C_6H_5
H	C_2H_5	$(CH_2)_3$—S—CH_2	4-FC_6H_4
H	CH_3	$(CH_2)_3$—S—	C_5H_8
H	C_2H_5	$(CH_2)_3$—S—$(CH_2)_2$	CH_3
H	H	$(CH_2)_3$—S—$(CH_2)_4$	C_6H_5
H	CH_3	$CH(CH_3)(CH_2)_2$—S—	4-piperidyl
H	CH_3	$CH(CH_3)(CH_2)_2$—S—	4-(C_6H_5)C_6H_{10}
H	CH_3	$CH(CH_3)(CH_2)_2$—S—$(CH_2)_4$	4-pyridyl
H	CH_3	$CH(CH_3)(CH_2)_2$—S—$(CH_2)_4$	C_6H_5
H	C_2H_5	$CH(C_2H_5)(CH_2)_2$—S—	C_6H_{11}
H	CH_3	$CH(C_2H_5)(CH_2)_2$—S—$(CH_2)_2$—$CH(CH_3)$	CH_3
H	H	$CH(C_2H_5)(CH_2)_2$—S—$CH(CH_3)$	4-ClC_6H_4
H	H	$CH(CH_3)(CH_2)_3$—S—$(CH_2)_4$	4-FC_6H_4
H	CH_3	$CH(CH_3)(CH_2)_3$—S—$(CH_2)_4$	4-pyridyl
H	H	$CH(CH_3)CH_2$—O—$(CH_2)_6$	CH_3
H	CH_3	$CH(CH_3)CH_2$—O—$(CH_2)_6$	C_6H_5
H	H	$CH(CH_3)CH_2$—O—$(CH_2)_4$	CH_3
H	H	$CH(CH_3)CH_2$—O—$CH(CH_3)CH_2$	C_6H_5
H	CH_3	$CH(CH_3)CH_2$—O—$CH(CH_3)CH_2$	C_6H_5
H	C_2H_5	$CH(CH_3)CH_2$—O—$CH(CH_3)CH_2$	C_6H_5
H	CH_3	$CH(CH_3)CH_2$—O—CH_2	4-FC_6H_4
H	CH_3	$CH(CH_3)CH_2$—O—$(CH_2)_2$	4-pyridyl
H	H	$CH(CH_3)CH_2$—O—$CH(CH_3)$	CH_3

R_5	R_4	Z	W
H	H	$CH_2CH(CH_3)—O—CH_2$	CH_3
H	C_2H_5	$CH_2CH(CH_3)—O—CH_2$	CH_3
H	CH_3	$CH_2CH(CH_3)—O—(CH_2)_6$	CH_3
H	CH_3	$CH_2CH(CH_3)—O—CH(CH_3)CH_2$	C_6H_5
H	H	$CH_2CH(CH_3)—O—(CH_2)_2$	$4\text{-}FC_6H_4$
H	CH_3	$C(CH_3)_2(CH_2)_6$	H
H	C_2H_5	$C(CH_3)_2(CH_2)_6$	H
CH_3	CH_3	$CH(CH_3)(CH_2)_3$	C_6H_5
C_2H_5	C_2H_5	$CH(CH_3)(CH_2)_3$	C_6H_5
C_2H_5	CH_3	$CH(CH_3)(CH_2)_4$	C_6H_5
CH_3	CH_3	$CH(CH_3)(CH_2)_3$	C_6H_5
H	$CH_2C_6H_5$	$(CH_2)_3$	C_6H_5
H	$n\text{-}C_6H_{13}$	$(CH_2)_4$	C_6H_5
CH_3	C_2H_5	$(CH_2)_4$	C_6H_5
H	$(CH_2)_4C_6H_5$	$(CH_2)_2CH(C_2H_5)$	C_6H_5
CH_3	CH_3	$C(CH_3)_2$	C_6H_5
CH_3	CH_3	$C(CH_3)_2(CH_2)_3$	C_6H_5
C_2H_5	C_2H_5	$(CH_2)_6$	C_6H_5
CH_3	CH_3	$(CH_2)_6$	C_6H_5
CH_3	CH_3	$CH(CH_3)(CH_2)_7$	C_6H_5
H	$n\text{-}C_4H_9$	CH_2	C_6H_5
CH_3	CH_3	$CH(CH_3)(CH_2)_3$	$4\text{-}FC_6H_4$
CH_3	$n\text{-}C_6H_{13}$	$CH(CH_3)CH_2$	$4\text{-}FC_6H_4$
H	$(CH_2)_2C_6H_5$	$CH(CH_3)(CH_2)_2CH(CH_3)$	C_6H_5
H	CH_3	CH_2	C_6H_5
H	$CH_2C_6H_5$	$(CH_2)_3$	C_5H_9
CH_3	CH_3	$CH(CH_3)CH_2$	C_5H_9
CH_3	$CH_2C_6H_5$	$CH(CH_3)(CH_2)_2$	C_5H_9
CH_3	CH_3	$CH(CH_3)CH_2$	C_3H_5
H	$(CH_2)_3C_6H_5$	$CH(CH_3)(CH_2)_5$	C_6H_{11}
CH_3	CH_3	$CH(CH_3)(CH_2)_5$	C_6H_{11}
CH_3	$n\text{-}C_4H_9$	$(CH_2)_4$	C_3H_5

R_5	R_4	Z	W
CH_3	CH_3	$(CH_2)_9$	C_6H_{11}
CH_3	CH_3	$(CH_2)_3$	2-pyridyl
CH_3	$CH_2C_6H_5$	$(CH_2)_3$	4-pyridyl
CH_3	CH_3	$(CH_2)_4$	4-pyridyl
C_2H_5	C_2H_5	$(CH_2)_4$	3-pyridyl
CH_3	CH_3	$CH(CH_3)CH(C_2H_5)CH_2$	4-pyridyl
H	n-C_5H_{11}	$CH(C_2H_5)(CH_2)_3$	3-pyridyl
H	i-C_3H_7	$CH(CH_3)(CH_2)_2$	4-piperidyl
CH_3	CH_3	$CH(C_2H_5)(CH_2)_2$	2-piperidyl
CH_3	CH_3	$CH(CH_3)(CH_2)_2CH(CH_3)$	4-piperidyl
CH_3	CH_3	$CH(CH_3)(CH_2)_2$	C_7H_{13}
H	n-C_4H_9	$CH(CH_3)(CH_2)_2$	C_7H_{13}
CH_3	CH_3	$CH(CH_3)CH_2—O—(CH_2)_2$	C_6H_5
CH_3	$CH_2C_6H_5$	$(CH_2)_4$	CH_3
CH_3	CH_3	$CH(CH_3)CH(CH_3)—(CH_2)_5$	H
C_2H_5	C_2H_5	$CH(CH_3)CH(CH_3)—(CH_2)_5$	H
CH_3	CH_3	CH_2	H
CH_3	C_2H_5	$(CH_2)_3$	CH_3
H	n-C_6H_{13}	$(CH_2)_6$	CH_3
CH_3	$(CH_2)_3C_6H_5$	$CH(CH_3)$	CH_3
CH_3	CH_3	$(CH_2)_3$	H
H	n-C_4H_9	$CH(CH_3)$	C_6H_{11}
CH_3	CH_3	$(CH_2)_3—O—$	C_6H_5
CH_3	CH_3	$(CH_2)_3—O—$	4-FC_6H_4
CH_3	CH_3	$(CH_2)_3—O—$	C_6H_{11}
C_2H_5	C_2H_5	$(CH_2)_3—O—$	C_4H_7
H	$CH_2C_6H_5$	$(CH_2)_3—O—$	CH_3
CH_3	CH_3	$(CH_2)_3—O—$	4-(4-FC_6H_4)C_6H_{10}
C_2H_5	C_2H_5	$(CH_2)_3—O—(CH_2)_2$	4-ClC_6H_4
CH_3	CH_3	$(CH_2)_3—O—CH(CH_3)$	4-piperidyl
H	n-C_5H_{11}	$CH(CH_3)(CH_2)_2—O—$	C_6H_5
CH_3	CH_3	$CH(CH_3)(CH_2)_2—O—CH_2$	CH_3

R_5	R_4	Z	W
CH_3	CH_3	$CH(CH_3)(CH_2)_2$—O—$(CH_2)_4$	C_6H_5
CH_3	CH_3	$CH(CH_3)(CH_2)_2$—O—CH—(CH_3)	C_7H_{13}
CH_3	CH_3	$CH(CH_3)(CH_2)_2$—O—CH_2—$CH(C_2H_5)$	CH_3
CH_3	CH_3	$(CH_2)_4$—O—	C_6H_5
C_2H_5	C_2H_5	$(CH_2)_4$—O—$CH(CH_3)CH_2$	3-piperidyl
CH_3	C_2H_5	$(CH_2)_4$—O—CH_2	4-FC_6H_4
H	n-C_3H_7	$CH(CH_3)(CH_2)_3$—O—	2-(4-FC_6H_5)C_5H_8
CH_3	CH_3	$CH(CH_3)(CH_2)_3$—O—$(CH_2)_2$	C_6H_5
CH_3	CH_3	$CH(C_2H_5)(CH_2)_2$—O—$CH(CH_3)$	4-piperidyl
CH_3	CH_3	$CH(C_2H_5)(CH_2)_2$—O—	C_3H_5
CH_3	CH_3	$CH(C_2H_5)(CH_2)_2$—O—	2-(4-FC_6H_{11})C_7H_{12}
CH_3	CH_3	$(CH_2)_3$—S	C_6H_5
C_2H_5	C_2H_5	$(CH_2)_3$—S—CH_2	4-FC_6H_4
CH_3	CH_3	$(CH_2)_3$—S—	C_5H_9
CH_3	$CH_2C_6H_5$	$(CH_2)_3$—S—$(CH_2)_4$	C_6H_5
CH_3	CH_3	$CH(CH_3)(CH_2)_2$—S—	4-piperidyl
CH_3	CH_3	$CH(CH_3)(CH_2)_2$—S—$(CH_2)_4$	4-pyridyl
CH_3	CH_3	$CH(CH_3)(CH_2)_2$—S—$(CH_2)_4$	C_6H_5
C_2H_5	C_2H_5	$CH(C_2H_5)(CH_2)_2$—SO	C_6H_{11}
H	n-C_6H_{13}	$CH(C_2H_5)(CH_2)_2$—S—$CH(CH_3)$	4-ClC_6H_4
CH_3	n-C_4H_9	$CH(CH_3)(CH_2)_3$—S—$(CH_2)_4$	4-FC_6H_4
CH_3	CH_3	$CH(CH_3)(CH_2)_3$—S—$(CH_2)_4$	4-pyridyl
CH_3	CH_3	$CH(CH_3)CH_2$—O—$(CH_2)_6$	C_6H_5
CH_3	CH_3	$C(CH_3)_2(CH_2)_6$	H
C_2H_5	C_2H_5	$C(CH_3)_2(CH_2)_6$	H

Of course, when Z contains an ether or thioether linkage, the procedure of Example 14 is used for the cyclization step.

Example 19.

d,l-*5-Hydroxy-2-methyl-7-(2-heptyloxy)-4-oxo-1,2,3,4-tetrahydroquinoline.*

Potassium hydroxide pellets (325 mg., 52 mmole) is added to a solution of *d,l*-5,7-dihydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline (1.0 g., 52 mmole) in N,N-dimethylformamide (10 ml.). The mixture is slowly heated to 100°C. and to the resulting solution *d,l*-2-bromoheptane (1.08 g., 60 mmole) is added all at once with good stirring. After 10 minutes additional potassium hydroxide (160 mg.) is added followed by additional *d,l*-2-bromoheptane (500 mg.). The addition of potassium hydroxide and *d,l*-2-bromoheptane was repeated two more times using 80 mg.

potassium hydroxide and 250 mg. *d,l*-2-bromoheptane each time. The reaction mixture is stirred an additional 10 minutes and is then cooled. Chloroform (50 ml.) and aqueous sodium hydroxide (25 ml. of 1N) are added, the mixture stirred for 10 minutes and the layers separated. The chloroform extraction is repeated, the extracts combined, dried ($MgSO_4$) and concentrated under reduced pressure to a dark oil. The oil is chromatographed on silica gel (120 g.) using benzene as solvent. Fractions of 30 ml. each are collected. The 12th-18th fractions are combined and concentrated under reduced pressure to a light yellow oil (850 mg.) which crystallizes upon standing. The desired product is separated by filtration and recrystallized from hot hexane, m.p. 76°—77°C.

The above procedure is repeated on a 20-fold scale but using benzeneethyl acetate (9:1) as chromatographic solvent. Fractions of 750 ml. each are collected. Combination of the 2nd-6th fractions affords 32 g. of oil which partially crystallizes from hexane upon standing and cooling to give 18.2 g. of product. An additional 3.2 g. is obtained by concentrating the mother liquor and allowing it to crystallize by standing in the cold. Total yield = 21.4 g.

Analysis: Calc'd for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81%
Found: C, 69.82; H, 8.67; N, 4.93%

m/e — 291 (m^+)

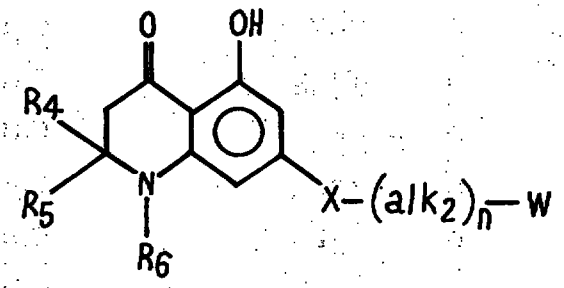
IR (KBr): 6.01 μ (=O)

In like manner, 5,7-dihydroxy-4-oxo-1,2,3,4-tetrahydroquinoline converted to *d,l*-5-hydroxy-7-(2-heptyloxy)-4-oxo-1,2,3,4-tetrahydroquinoline, an oil.

^{1}H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 13.3 (s, 1H, phenolic), 5.5 and 5.7 (d, 2H, J = 2Hz, aromatic, 4.6 (bs, 1H, —NH), 4.1—4.6 (m, 1H, —O—CH—), 3.3 (t, 2H, J = 7Hz, —CH_2—), 2.6 (t, 2H, J = 7Hz, —CH_2—), 2.0—0.7 (m, remaining protons).

Example 20.

The following compounds are prepared according to the procedure of Example 19 but using the appropriate Br—$(alk_2)_n$—W reactant and the appropriate 5,7-dihydroxy-2-R_4R_5-4-oxo-1,2,3,4-tetrahydroquinoline or 5-hydroxy-7-thiol-2-R_4R_5-4-oxo-1,2,3,4-tetrahydroquinoline.



R_5	R_4	X	—alk_2—	W	R_6
H	H	O	CH_2	H	H
H	CH_3	O	CH_2	H	H
H	CH_3	O	$(CH_2)_2$	H	H
H	H	O	$(CH_2)_4$	H	CH_3
H	CH_3	O	$(CH_2)_6$	H	H
H	CH_3	O	$(CH_2)_9$	H	H
H	H	O	$CH(CH)_3CH_2$	H	C_2H_5
H	CH_3	O	$CH(CH_3)(CH_2)_3$	H	CH_3
H	H	O	$CH(CH_3)(CH_2)_4$	CH_3	H

R_5	R_4	X	—alk_2—	W	R_6
H	C_2H_5	O	CH_2	C_6H_5	$CH_2C_6H_5$
H	H	O	$(CH_2)_2$	C_6H_5	CH_2COOH
H	CH_3	O	$(CH_2)_4$	C_6H_5	CH_2COOH
H	C_2H_5	O	CH_2	4-ClC_6H_4	H
H	H	O	CH_2	4-FC_6H_4	H
H	CH_3	O	$CH(CH_3)CH_2$	C_6H_5	CH_3
H	H	O	$CH(CH_3)(CH_2)_2$	C_6H_5	CH_3
H	CH_3	O	$CH(CH_3)(CH_2)_3$	C_6H_5	H
H	C_2H_5	O	$(CH_2)_7$	C_6H_5	H
H	H	O	$CH(CH_3)CH(CH_3)(CH_2)_4$	CH_3	H
H	H	O	$(CH_2)_2$	4-pyridyl	C_2H_5
H	CH_3	O	$(CH_2)_3$	4-pyridyl	H
H	C_2H_5	O	$(CH_2)_3$	3-pyridyl	n-C_4H_9
H	CH_3	O	$CH(CH_3)CH_2$	2-pyridyl	H
H	H	O	CH_2	C_3H_5	H
H	CH_3	O	CH_2	C_3H_5	H
H	CH_3	O	$CH(CH_3)$	C_4H_7	H
H	CH_3	O	$(CH_2)_2$	C_5H_9	H
H	CH_3	O	CH_2	C_6H_{11}	H
H	CH_3	O	$(CH_2)_3$	C_6H_{11}	H
H	C_2H_5	O	$(CH_2)_3$	C_5H_9	H
H	CH_3	O	$(CH_2)_4$	C_7H_{13}	H
H	H	O	—	C_6H_5	H
H	CH_3	O	—	C_6H_5	CH_3
H	H	O	—	4-FC_6H_4	H
H	H	O	—	4-ClC_6H_4	$(CH_2)_2C_6H_5$
H	C_2H_5	O	—	C_6H_5	H
H	H	O	—	C_5H_9	H
H	C_2H_5	O	—	C_5H_9	H
H	CH_3	O	—	C_6H_{11}	H
H	H	O	—	C_7H_{13}	H
H	H	O	—	2-$(C_6H_5)C_3H_4$	H

R_5	R_4	X	—alk_2—	W	R_6
H	C_2H_5	O	—	2-(C_6H_5)C_3H_4	CH_3
H	C_2H_5	O	—	4-(C_6H_5)C_6H_{10}	H
H	H	O	—	3-(C_6H_5)C_7H_{12}	H
H	H	O	—	4-pyridyl	C_2H_5
H	CH_3	O	—	4-pyridyl	H
H	C_2H_5	O	—	4-piperidyl	H
H	CH_3	O	—	2-pyridyl	H
H	CH_3	O	—	3-piperidyl	H
H	H	S	CH_2	H	H
H	CH_3	S	CH_2	H	H
H	H	S	$(CH_2)_3$	H	$(CH_2)_2COOH$
H	CH_3	S	$(CH_2)_3$	H	$(CH_2)_2COOH$
H	H	S	$(CH_2)_5$	H	H
H	CH_3	S	$(CH_2)_5$	H	H
H	C_2H_5	S	$(CH_2)_4$	H	H
H	H	S	$(CH_2)_6$	H	H
H	CH_3	S	$CH(CH_3)(CH_2)_5$	H	$(CH_2)_3COOH$
H	H	S	$CH(CH_3)(CH_2)_3$	H	H
H	CH_3	S	CH_2	C_3H_5	H
H	H	S	CH_2	C_6H_{11}	H
H	CH_3	S	$(CH_2)_3$	C_6H_{11}	H
H	C_2H_5	S	$(CH_2)_4$	C_7H_{13}	H
H	H	S	$CH(CH_3)$	C_4H_7	H
H	H	S	$CH(CH_3)CH(CH_3)(CH_2)_4$	CH_3	H
H	CH_3	S	$CH(CH_3)CH(CH_3)(CH_2)_4$	CH_3	H
H	H	S	$C(CH_3)_2(CH_2)_5$	CH_3	H
H	CH_3	S	$C(CH_3)_2(CH_2)_5$	CH_3	H
H	CH_3	S	CH_2	C_6H_5	H
H	CH_3	S	$(CH_2)_4$	C_6H_5	H
H	H	S	$CH(CH_3)(CH_2)_2$	C_6H_5	H
H	CH_3	S	$CH(CH_3)(CH_2)_3$	C_6H_5	CH_3
H	CH_3	S	CH_2	4-FC_6H_4	H

R_5	R_4	X	—alk_2—	W	R_6
H	H	S	CH_2	4-ClC_6H_4	H
H	CH_3	S	$(CH_2)_3$	4-pyridyl	H
H	C_2H_5	S	$CH(CH_3)CH_2$	2-pyridyl	H
H	H	S	—	C_6H_5	H
H	CH_3	S	—	4-FC_6H_5	H
H	C_2H_5	S	—	C_6H_9	H
H	CH_3	S	—	C_6H_{11}	H
H	H	S	—	4-pyridyl	H
H	CH_3	S	—	4-piperidyl	$CH_2C_6H_5$
H	CH_3	S	—	C_7H_{13}	H
H	CH_3	S	—	2-$(C_6H_5)C_3H_4$	H
H	CH_3	S	—	4-$(C_6H_5)C_6H_{10}$	H
H	H	S	—	4-ClC_6H_4	H
H	H	S	$CH(CH_3)(CH_2)_4$	CH_3	CH_3
H	CH_3	S	$CH(CH_3)(CH_2)_3$	C_6H_5	CH_3
H	H	S	$C(CH_3)_2(CH_2)_5$	CH_3	i-C_3H_7
H	C_2H_5	S	$(CH_2)_4$	CH_3	$(CH_2)_3C_6H_5$
H	CH_3	O	$CH(CH_3)(CH_2)_4$	CH_3	$(CH_2)_4C_6H_5$
H	CH_3	O	$CH(CH_3)(CH_2)_3$	C_6H_5	n-C_4H_9
H	CH_3	O	$CH(CH_3)(CH_2)_3$	C_6H_5	CH_2COOH
H	H	O	$CH(CH_3)(CH_2)_3$	C_6H_5	CH_2COOH
H	H	O	$CH(CH_3)(CH_2)_3$	C_6H_5	$(CH_2)_4COOH$
CH_3	CH_3	O	CH_2	H	H
C_2H_5	CH_3	O	$(CH_2)_4$	H	CH_3
CH_3	CH_3	O	$(CH_2)_8$	H	H
CH_3	CH_3	O	$CH(CH_3)(CH_2)_3$	CH_3	H
CH_3	CH_3	O	$CH(CH_3)(CH_2)_4$	CH_3	H
CH_3	n-C_6H_{13}	O	$CH(CH_3)CH(CH_3)(CH_2)_4$	CH_3	H
C_2H_5	C_2H_5	O	$C(CH_3)_2(CH_2)_4$	CH_3	H
CH_3	CH_3	O	$CH(CH_3)(CH_2)_3$	C_6H_5	H
H	n-C_6H_{13}	O	$CH(CH_3)(CH_2)_4$	CH_3	CH_3
CH_3	CH_3	O	$CH(CH_3)(CH_2)_3$	4-FC_6H_4	n-C_3H_7

R_5	R_4	X	—alk_2—	W	R_6
H	CH_3	O	$CH(CH_3)(CH_2)_4$	CH_3	n-C_6H_{13}
H	C_2H_5	O	$CH(CH_3)(CH_2)_3$	CH_3	CH_2COOH
H	CH_3	O	$CH(CH_3)(CH_2)_3$	4-ClC_6H_4	$(CH_2)_4COOH$
CH_3	CH_3	O	$(CH_2)_3$	4-pyridyl	$CH_2C_6H_5$
CH_3	$CH_2C_6H_5$	O	$CH(CH_3)(CH_2)_3$	3-pyridyl	H
CH_3	n-C_4H_9	O	—	C_6H_5	H
CH_3	$(CH_2)_3C_6H_5$	O	—	4-FC_6H_5	$CH_2C_6H_5$
CH_3	CH_3	O	—	4-pyridyl	$(CH_2)_4C_6H_5$
CH_3	CH_3	O	—	C_5H_9	H
C_2H_5	C_2H_5	O	—	C_7H_{13}	H
H	C_2H_5	O	—	3-piperidyl	H
CH_3	CH_3	O	—	2-$(C_6H_5)C_3H_4$	CH_3
CH_3	CH_3	O	—	3-$(C_6H_5)C_7H_{12}$	H
CH_3	CH_3	O	CH_2	C_3H_5	H
CH_3	CH_3	O	$(CH_2)_3$	C_6H_{11}	$(CH_2)_2COOH$
CH_3	C_2H_5	O	$(CH_2)_4$	C_7H_{13}	$(CH_2)_4COOH$
CH_3	CH_3	S	—	C_6H_5	n-C_5H_{11}
CH_3	CH_3	S	—	4-ClC_6H_4	H
CH_3	CH_3	S	—	C_7H_{13}	H
CH_3	CH_3	S	—	4-$(C_6H_5)C_6H_{10}$	H
H	n-C_4H_9	S	—	C_6H_5	H
CH_3	$(CH_2)_3C_6H_5$	S	—	4-pyridyl	$CH_2C_6H_5$
CH_3	$CH_2C_6H_5$	S	—	C_6H_{11}	CH_3
C_2H_5	$(CH_2)_2C_6H_5$	S	—	4-FC_6H_4	CH_2COOH
CH_3	CH_3	S	—	4-$(C_6H_5)C_6H_{10}$	$(CH_2)_4COOH$
CH_3	n-C_6H_{13}	S	—	C_6H_5	H
CH_3	$CH_2C_6H_5$	S	—	C_6H_5	H
C_2H_5	C_2H_5	S	CH_2	H	H
CH_3	CH_3	S	$(CH_2)_5$	H	CH_3
CH_3	CH_3	S	$(CH_2)_9$	H	i-C_3H_7
CH_3	CH_3	S	$C(CH_3)_2(CH_2)_6$	H	$(CH_2)_3C_6H_5$
CH_3	CH_3	S	$CH(CH_3)(CH_2)_4$	CH_3	$CH_2C_6H_5$

R_5	R_4	X	—alk_2—	W	R_6
CH_3	CH_3	S	$CH(CH_3)(CH_2)_3$	C_6H_5	H
C_2H_5	n-C_4H_9	S	$CH(CH_3)(CH_2)_3$	C_6H_{11}	i-C_3H_7
H	$CH_2C_6H_5$	S	$C(CH_3)_2(CH_2)_6$	H	H
CH_3	$(CH_2)_2C_6H_5$	S	2-$(C_6H_5)C_3H_4$	H	H
H	n-C_3H_7	O	$C(CH_3)_2(CH_2)_6$	H	H
C_2H_5	n-C_4H_9	O	CH_2	4-pyridyl	H
CH_3	$(CH_2)_4C_6H_5$	O	$(CH_2)_4$	CH_3	H
C_2H_5	$(CH_2)_3C_6H_5$	S	—	C_6H_5	H
CH_3	CH_3	O	CH_2	C_6H_5	n-C_6H_{13}
CH_3	$CH_2C_6H_5$	O	$(CH_2)_6$	4-FC_6H_5	n-C_4H_9
CH_3	n-C_4H_9	O	$CH(CH_3)(CH_2)_3$	H	CH_3
CH_3	CH_3	O	$C(CH_3)_2(CH_2)_5$	CH_3	CH_2COOH

Example 21.

d,l-*5-Hydroxy-2-methyl-7-(5-phenyl-2-pentyloxy)-4-oxo-1,2,3,4-tetrahydroquinoline.*

A mixture of 5-phenyl-2-(R,S)-pentanol (16.4 g., 100 mmole), triethylamine (28 ml., 200 mmole) and dry tetrahydrofuran (80 ml.) under a nitrogen atmosphere is cooled in an ice/water bath. Methanesulfonyl chloride (8.5 ml., 110 mM) in dry tetrahydrofuran (20 ml.) is added dropwise at such a rate that the temperature holds essentially constant. The mixture is allowed to warm to room temperature and is then filtered to remove triethylamine hydrochloride. The filter cake is washed with dry tetrahydrofuran and the combined wash and filtrate evaporated under reduced pressure to give the product as an oil. The oil is dissolved in chloroform (100 ml.) and the solution washed with water (2 x 100 ml.) and then with saturated brine (1 x 20 ml.). Evaporation of the solvent affords 21.7 g. (89.7%) yield of the mesylate of *d,l*-5-phenyl-2-pentanol which is used in the next step without further purification.

A mixture of *d,l*-5,7-dihydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline (1.0 g., 5.2 mmole), potassium carbonate (14.35 g., 0.104 mole), N,N-dimethylformamide (60 ml.) and *d,l*-5-phenyl-2-pentanol mesylate (13.68 g., 57 mmole), under a nitrogen atmosphere, is heated to 80°—82°C. in an oil bath for 1.75 hours. The mixture is cooled to room temperature and then poured into ice/water (300 ml.). The aqueous solution is extracted with ethyl acetate (2 x 50 ml.) and the combined extracts washed successively with water (3 x 50 ml.) and saturated brine (1 x 50 ml.). The extract is then dried ($MgSO_4$), decolorized with charcoal and evaporated to give the product.

m/e — 339 (m^+)

The above procedure is repeated but using 114.8 g. (0.594 mole) of *d,l*-5,7-dihydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline, 612 ml. of N,N-dimethylformamide, 174.8 g. (1.265 moles) of potassium carbonate and 165.5 g. (0.638 mole) of *d,l*-5-phenyl-2-pentanol mesylate. The reaction mixture is cooled and poured onto ice water (4 liters) and the aqueous solution extracted with ethyl acetate (2 x 4 liters). The combined extract is washed with water (4 x 2 liters), brine (1 x 2 liters) and dried ($MgSO_4$). Evaporation affords 196 g. of the title product. It is used without further purification.

^1H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 12.73 (s, 1H, OH), 7.22 (s, 5H, aromatic), 5.80 (d, J=3 H_3, 1H, meta H), 5.58 (d, J=3 H_3, 1H, meta H), 1.25 (d, 6H, CH_3—CH—N and CH_3—CH—O—), 1.41—4.81 (m, 11H, remaining protons).

Example 22.

d,l-5-Hydroxy-7-(5-phenyl-2-pentyloxy)-4-oxo-1,2,3,4-tetrahydroquinoline

Repetition of the procedure of Example 21 but using 5,7-dihydroxy-4-oxo-1,2,3,4-tetrahydroquinoline in place of the 5,7-dihydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline affords *d,l*-5-hydroxy-7-(5-phenyl-2-pentyloxy)-4-oxo-1,2,3,4-tetrahydroquinoline as an oil in 74% yield.

m/e — 325 (m^+)

Analysis: Calc'd for $C_{20}H_{23}NO_3$: C, 73.70; H, 7.12; N, 4.31%
Found: C, 73.69; H, 7.15; N, 4.08%

^1H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 12.6 (bs, 1H, phenolic), 7.3 (s, 5H, aromatic), 5.8 (d, 1H, aromatic, J = 2Hz), 5.6 (d, 1H, aromatic, J = 2Hz), 4.7—4.1 (m, 2H, NH and O—CH), 3.5 (t, 2H, CH_2, J = 7Hz), 3.1—2.1 (m, 4H, 2—CH_2—), 2.1—1.5 (m, 4H, 2—CH_2), 1.3 (d, 3H, —CH—CH_3, J = 6Hz).

Similarly, *d,l*-5,7-dihydroxy-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline (27 g., 0.14 mole) is alkylated with 4-phenylbutyl methanesulfonate (35.2 g., 0.154 mole) to yield 41.1 g. (90%) of the desired *d,l*-5-hydroxy-2-methyl-7-(4-phenylbutyloxy)-4-oxo-1,2,3,4-tetrahydroquinoline, m.p. 88°—90°C. Recrystallization from ethyl aetate-hexane (1:2) gives the analytical sample, m.p. 90°—91°C.

Calc'd for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12; N, 4.30%
Found: C, 73.60; H, 7.09; N, 4.26%

m/e — 325 (m^+)

^1H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 12.58 (s, 1H, —OH), 7.21 (s, 5H, C_6H_5), 5.74 (d, J = 2.5 Hz, 1H, meta H), 5.5 (d, J = 2.5Hz, 1H, meta H), 4.36 (bs, 1H, NH), 3.33—4.08 (m, 3H, —O—CH_2, —CH—N), 2.29—2.83 (m, 4H, —CH_2—C=O, C_6H_5—CH_2), 1.51—1.92 (m, 4H, —$[CH_2]_2$—), 1.23 (d, 3H, CH_3—).

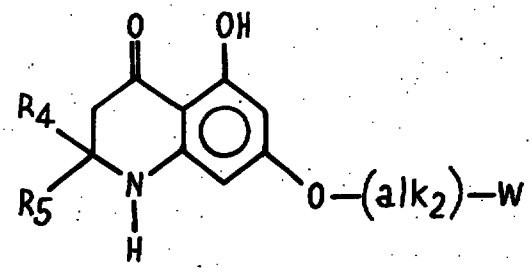
In like manner, alkylation of *d*-5,7-dihydroxy-4-oxo-1,2,3,4-tetrahydroquinoline with *d*-2-octylmethanesulfonate gives *d*-5-hydroxy-2-methyl-7-(2-(R)-octyloxy)-4-oxo-1,2,3,4-tetrahydroquinoline, m.p. 64°—68°C.

$[\alpha]_D^{25}$ = +110.2° (c=1.0, $CHCl_3$).

and alkylation of *d,l*-5,7-dihydroxy-2-propyl-4-oxo-1,2,3,4-tetrahydroquinoline with *d,l*-5-phenyl-2-pentanol mesylate gives *d,l*-5-hydroxy-7-(5-phenyl-2-pentyloxy)-2-propyl-4-oxo-1,2,3,4-tetrahydroquinoline; m/e — 367 (m^+).

Example 23.

The following compounds are prepared from appropriate reactants by the procedure of Example 21. The necessary alkanol reactants not previously described in the literature are prepared from appropriate aldehydes or ketones by the procedures of Preparations G and H.



R_5	R_4	alk_2	W
H	CH_3	$CH_2C(CH_3)_2(CH_2)_4$	CH_3
H	CH_3	$CH_2CH(CH_3)(CH_2)_2CH(CH_3)CH_2$	CH_3
H	CH_3	$CH(CH_3)CH_2CH(CH_3)CH_2CH(CH_3)$	CH_3
H	H	$CH(CH_3)(CH_2)_2C(CH_3)_2$	CH_3
H	C_2H_5	$CH_2CH(C_2H_5)$	C_6H_5

R_5	R_4	alk_2	W
H	CH_3	$CH_2CH_2CH(CH_3)$	C_6H_5
H	CH_3	$(CH_2)_7$	C_6H_5
H	H	$CH(CH_3)(CH_2)_5$	C_6H_5
H	C_2H_5	$(CH_2)_9$	C_6H_5
H	H	$(CH_2)_9$	CH_3
H	H	$CH(CH_3)CH_2$	2-pyridyl
H	C_2H_5	$(CH_2)_2$	2-pyridyl
H	C_2H_5	$(CH_2)_4$	2-pyridyl
H	H	$(CH_2)_3$	2-piperidyl
H	CH_3	$(CH_2)_3$	4-piperidyl
H	CH_3	$(CH_2)_3$	$4\text{-}FC_6H_4$
H	H	$(CH_2)_3$	$4\text{-}ClC_6H_4$
H	C_2H_5	$(CH_2)_4$	$4\text{-}FC_6H_4$
H	H	$CH(CH_3)(CH_2)_2$	2-pyridyl
H	C_2H_5	$CH(CH_3)(CH_2)_2$	3-pyridyl
H	CH_3	$CH_2C(CH_3)_2$	C_6H_5
H	CH_3	$CH(CH_3)(CH_2)_3$	4-pyridyl
H	CH_3	$CH(CH_3)(CH_2)_2$	4-piperidyl
H	C_2H_5	$CH(C_2H_5)(CH_2)_2$	4-piperidyl
H	H	$CH(CH_3)(CH_2)_2$	$4\text{-}FC_6H_4$
H	CH_3	$CH(CH_3)(CH_2)_2$	$4\text{-}ClC_6H_4$
H	H	CH_2	C_6H_5
H	CH_3	CH_2	$4\text{-}FC_6H_4$
H	CH_3	—	$4\text{-}FC_6H_4$
H	C_2H_5	—	$4\text{-}ClC_6H_4$
H	H	—	$4\text{-}FC_6H_4$
H	CH_3	—	C_3H_5
H	H	—	C_3H_5
H	CH_3	—	C_4H_7
H	C_2H_5	—	C_5H_9
H	CH_3	—	C_6H_{11}
H	CH_3	—	C_7H_{13}

R_5	R_4	alk_2	W
H	CH_3	—	2-$(C_6H_5)C_3H_4$
H	CH_3	—	1-$(C_6H_5)C_4H_6$
H	CH_3	—	2-$(C_6H_5)C_5H_8$
H	CH_3	—	4-$(C_6H_5)C_6H_{10}$
H	C_2H_5	—	3-$(C_6H_5)C_6H_{10}$
H	CH_3	—	4-pyridyl
H	CH_3	—	4-piperidyl
H	CH_3	—	2-$(C_6H_5)C_6H_{10}$
H	H	—	4-$(C_6H_5)C_6H_{10}$
H	CH_3	—	3-$(C_6H_5)C_7H_{12}$
H	CH_3	$—CH_2—$	CH_3
H	CH_3	$—(CH_2)_3—$	CH_3
H	CH_3	$—(CH_2)_6—$	CH_3
H	CH_3	$—(CH_2)_9—$	CH_3
H	H	$—(CH_2)_6—$	CH_3
H	C_2H_5	$—(CH_2)_3—$	CH_3
H	CH_3	$—C(CH_3)_2(CH_2)_5—$	CH_3
H	CH_3	$—C(CH_3)_2(CH_2)_5—$	CH_3
H	CH_3	$—CH(CH_3)CH(CH_3)(CH_2)_4—$	CH_3
CH_3	CH_3	$—CH(CH_3)(CH_2)_3—$	C_6H_5
CH_3	CH_3	$—(CH_2)_4—$	C_6H_5
CH_3	CH_3	$—C(CH_3)_2(CH_2)_6—$	H
CH_3	CH_3	—	C_6H_5
CH_3	CH_3	—	4-ClC_6H_4
CH_3	CH_3	$—CH(CH_3)(CH_2)_2—$	2-pyridyl
H	$CH_2C_6H_5$	$—CH(CH_3)(CH_2)_4—$	H
H	$CH_2C_6H_5$	$—C(CH_3)_2(CH_2)_6—$	H
CH_3	$CH_2C_6H_5$	—	4-FC_6H_5
H	$(CH_2)_3C_6H_5$	$—CH_2—$	C_6H_5
H	$(CH_2)_4C_6H_5$	$—(CH_2)_6—$	CH_3
C_2H_5	C_2H_5	$—(CH_2)_4—$	C_6H_5
C_2H_5	CH_3	$—CH_2—$	4-FC_6H_5

R_3	R_4	alk_2	W
H	i-C_3H_7	—$CH(CH_3)(CH_2)_3$—	4-piperidyl
H	n-C_4H_9	—$CH(CH_3)CH(CH_3)(CH_2)_5$—	H
H	n-C_6H_{13}	—$C(CH_3)_2(CH_2)_6$	H
CH_3	n-C_6H_{13}	—$(CH_2)_3$—	CH_3
CH_3	CH_3	—	C_5H_9
CH_3	CH_3	—	4-$(C_6H_5)C_6H_{10}$

PREPARATION A.

2-Bromo-5-phenylpentane

To phosphorus pentabromide, prepared by addition of bromine (9.0 g.) in methylene chloride (10 ml.) to phosphorus tribromide (15.0 g.) in methylene chloride (15 ml.) at 0°C., is added 5-phenyl-2-pentanol (812 g.) in methylene chloride at 0°C. The mixture is stirred for 2.5 hours at 0°C. and is then allowed to warm to room temperature. Water (50 ml.) is added, the mixture stirred for one hour and the methylene chloride layer separated. The extraction is repeated and the combined extracts washed with water, saturated sodium bicarbonate solution, brine and then dried over magnesium sulfate. Concentration of the dried extracts gives 12.4 g. of title product as a light yellow oil.

NMR: $\delta^{TMS}_{CDCl_3}$ 1.6 (D,3,methyl,J = 7Hz), 1.6—2.0 (M,4,ethylene), 2.3—3.0 (bd,T,2,benzylic-methylene), 3.7—4.2 (M,1,methine), 6.9—7.4(M,5,aromatic).

PREPARATION B.

2-(3,5-Dimethoxyphenyl)-5-phenylpentane

A solution of 1-bromopropylbenzene (51.7 g.) in ether (234 ml.) is added dropwise over a 2-hour period to a refluxing mixture of magnesium (7.32 g.) in ether (78 ml.). The reaction mixture is refluxed for 30 minutes longer and then a solution of 3,5-dimethoxy-acetophenone (50 g.) in ether (78 ml.) is added dropwise and heated to reflux for 1.5 hours. The reaction is quenched by addition of saturated ammonium chloride (234 ml.), the ether layer is separated and the aqueous phase extracted with ether (3 x 200 ml.). The combined ether extracts are dried over magnesium sulfate and concentrated under vacuum to yield 81 g. of an oil. Forty grams of the oil is hydrogenated in a mixture containing ethanol (300 ml.), concentrated hydrochloric acid (2 ml.) and 5% palladium-on-carbon (5 g.). The catalyst is filtered off and the ethanol removed under vacuum. The residue is distilled under vacuum yielding 28 g. of 2-(3,5-dimethoxyphenyl)-5-phenylpentane (b.p. 0.125 mm., 154°—159°C.)

NMR: $\delta^{TMS}_{CDCl_3}$ 1.25 (d,3,α—CH_3), 1.3—2.1 (M,4,ethylene), 2.2—2.9 (M,3,benzylic-methylene,methinyl), 3.45 (S,6,methoxyl), 6.2—6.7 (M,3,aromatic), 7.2 (S,5,aromatic).

PREPARATION C.

2-(3,5-Dihydroxyphenyl)-5-phenylpentane

A mixture of 2-(3,5-dimethoxyphenyl)-5-phenylpentane (22 g.) and pyridine hydrochloride (94 g.) under nitrogen is heated to 190°C. for 2 hours with vigorous stirring. The reaction mixture is cooled, dissolved in 6N hydrochloric acid (200 ml.) and diluted with water to 600 ml. The aqueous solution is extracted with ethyl acetate (4 x 100 ml.), the ethyl acetate extracts dried over sodium sulfate and concentrated under vacuum to yield 24 g. of crude product. The product is purified by silica gel chromatography to yield 19.2 g. of 2-(3,5-dihydroxyphenyl)-5-phenylpentane as an oil.

NMR: $\delta^{TMS}_{CDCl_3}$ 1.1 (d,3,α-methyl), 1.35—1.65 (M,4,ethylene), 2.2—2.8 (M,3,benzylic-methylene,methinyl), 6.1—6.5 (M,3,aromatic), 6.65 (bd.S, 2, hydroxyl), 7—7.4 (M,5,aromatic).

Following the procedures of Preparations B and C, the compounds listed

below are prepared by substituting the appropriate 1-bromoalkylbenzene for 1-bromopropylbenzene:

2-(3,5-dihydroxyphenyl)-6-phenylhexane.

NMR: $\delta^{TMS}_{CDCl_3}$ 1.1 (D,3,α-methyl, J—7 cps), 1.0—1.9 [M,6,ØCH$_2$(CH$_2$)$_3$—CH(CH$_3$)—Ar], 2.2—2.8 (M,3,benzylic methylene,methinyl), 6.0 (bd.S, 2,phenolic OH), 6.2—6.4 (M,3,aromatic), 7.1—7.4 (M,5,aromatic).

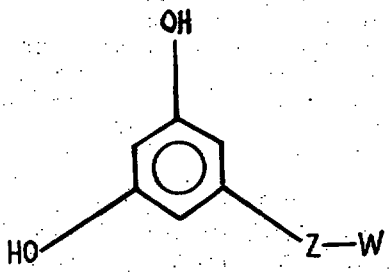
1-(3,5-dihydroxyphenyl)-2-phenylethane.

m.p.: 76°—77°C.

2-(3,5-dihydroxyphenyl-4-phenylbutane (an oil).

NMR: $\delta^{TMS}_{CDCl_3}$ 1.1, 1.25 (d,2,methyl), 1.45—2.0 (M,2,methylene), 2.15—2.7 (M,3,benzylic-methylene,methinyl), 6.3 (S,3,aromatic), 6.85 (S,2, hydroxyl-D$_2$O overlay), 7.1 (S,5,aromatic).

The following compounds are prepared in like manner from the appropriate alcohol and 3,5-dimethoxybenzaldehyde or 3,5-dimethoxyacetophenone by the methods of Preparations A, B and C:



Z	W
CH(CH$_3$)CH$_2$	C$_5$H$_9$
CH(CH$_3$)(CH$_2$)$_2$	C$_5$H$_9$
CH(CH$_3$)CH$_2$	C$_3$H$_5$
CH(CH$_3$)CH(CH$_3$)	C$_6$H$_{11}$
CH(CH$_3$)(CH$_2$)$_3$	C$_6$H$_{11}$
CH(CH$_3$)(CH$_2$)$_4$	C$_5$H$_9$
CH(CH$_3$)(CH$_2$)$_5$	C$_6$H$_{11}$
CH(C$_2$H$_5$)(CH$_2$)$_2$	C$_6$H$_{11}$
(CH$_2$)$_3$	C$_5$H$_9$
CH(C$_2$H$_5$)(CH$_2$)$_3$	C$_6$H$_5$
C(CH$_3$)$_2$	C$_6$H$_5$
(CH$_2$)$_4$	C$_6$H$_5$
(CH$_2$)$_2$CH(C$_2$H$_5$)	C$_6$H$_5$
CH(CH$_3$)CH$_2$CH(C$_2$H$_5$)	C$_6$H$_5$

PREPARATION D.

1-(3,5-Dihydroxyphenyl)-2-methyl-4-phenylbutane

A solution of n-butyl lithium (29 ml. of 2.2 M) is added dropwise to 3,5-dimethoxybenzyl triphenylphosphonium bromide (31.5 g.) in tetrahydrofuran (200 ml.) with stirring and the resulting deep red solution is stirred for one-half hour.

Benzyl acetone (9.4 g.) is added dropwise and the reaction mixture stirred for 12 hours. It is then adjusted to pH 7 by addition of acetic acid and concentrated under reduced pressure. The residue is extracted with methylene chloride and the extract evaporated to give crude 1-(3,5-dimethoxyphenyl)-2-methyl-4-phenyl-1-butene as an oil. It is purified by chromatography on silica gel (400 g.) and elution with benzene. Yield: 10 g. as an oil.

NMR: $\delta^{TMS}_{CDCl_3}$ 1.95 (S,3), 2.3—3.1 (M,4), 3.8 (S,6), 6.15—6.6 (M,3), 7.1—7.5 δ(M,6).

The 1-(3,5-dimethoxyphenyl)-2-methyl-4-phenyl-1-butene (9.4 g.) thus prepared is dissolved in ethanol (250 ml.) and catalytically hydrogenated at 45 p.s.i. in the presence of palladium-on-charcoal (1 g. of 10%) and concentrated hydrochloric acid (1 ml.). Yield: 9.4 g. of 1-(3,5-dimethoxyphenyl)-2-methyl-4-phenylbutane as an oil.

NMR: $\delta^{TMS}_{CDCl_3}$ 0.9 (d,3), 1.35—1.95 (M,3), 2.2—2.9 (M,4), 3.75 (S,6), 6.35 (S,3), 7.25 δ(S,5).

It is demethylated according to the procedure of Preparation C to give 1-(3,5-dihydroxyphenyl)-2-methyl-4-phenylbutane.

The 3,5-dimethoxybenzyl triphenylphosphonium bromide is prepared by refluxing a mixture of 3,5-dimethoxybenzyl bromide (12 g.) and triphenylphosphine (14.2 g.) in acetonitrile (200 ml.) for one hour. The reaction mixture is then cooled and the crystalline product recovered by filtration, washed with ether and dried (20 g.); m.p. 269°—270°C.

PREPARATION E.

2-Methyl-2-(3,5-dihydroxyphenyl)-5-phenylpentane

To a solution of the Grignard reagent prepared from 2-phenylbromoethane (5.5 g.), magnesium (0.8 g.) and dry ether (60 ml.) is added a solution of 2-methyl-2-(3,5-dimethoxyphenyl)propionitrile (2.75 g.) in dry ether (20 ml.). The ether is distilled off and replaced by dry benzene (50 ml.) and the mixture refluxed for 48 hours. It is then decomposed by careful treatment with dilute sulfuric acid and heated on a steam bath for one hour. The mixture is then extracted with ether, the extract dried ($MgSO_4$) and concentrated to an oil. Distillation of the oil *in vacuo* affords 2-methyl-2-(3,5-dimethoxyphenyl)-5-phenyl-3-pentanone; b.p. 168° C./0.2 mm. (Yield: 2.32 g., 60%).

The thus-produced pentanone (58 g.) is dissolved in ethanol (400 ml.) and treated with sodium borohydride (10 g.) at room temperature. The reaction mixture is stirred for 12 hours and is then cooled and neutralized with 6N hydrochloric acid. The ethanol is removed under reduced pressure and the residue extracted with ether. The extract is dried ($MgSO_4$) and concentrated to give 2-methyl-2-(3,5-dimethoxyphenyl)-5-phenyl-3-pentanol as an oil (52 g., 88% yield).

The pentanol (16 g.) is taken up in ether (100 ml.) and reacted with powdered potassium (2.5 g.) in ether (200 ml.). Carbon disulfide (equimolar to the potassium) is added and the mixture stirred for a half-hour. Methyl iodide (9.0 g.) is then added and the reaction mixture stirred for 6 hours. The resulting suspension is filtered and the filtrate concentrated under reduced pressure. The residue is taken up in ethanol (150 ml.), Raney nickel added (25 g.) and the mixture refluxed for 18 hours. Evaporation of the alcohol and distillation of the residue gives 2-methyl-2-(3,5-dimethoxyphenyl)-5-phenyl-3-pentene.

The pentene derivative is catalytically hydrogenated according to the procedure of Preparation D and the resulting 2-methyl-2-(3,5-dimethoxyphenyl)-5-phenylpentane demethylated via the procedure of Preparation C to give the product.

PREPARATION F.

3,5-Dibenzyloxyacetophenone

Over a period of 1.5 hours, methyl lithium (531 ml. of a 2 molar solution, 1.06 M) is added under a nitrogen atmosphere to a rapidly stirring solution of 3,5-dibenzyloxybenzoic acid (175 g., 0.532 M) in ether (250 ml.)-tetrahydrofuran (1400 ml.) maintained at 15°—20°C. After stirring an additional 0.75 hour at 10°—15°C., water (600 ml.) is slowly added keeping the reaction temperature below 20°C. The aqueous layer is separated and extracted with ether (3 x 250 ml.). The organic phases are combined, washed with saturated sodium chloride solution (4 x 300 ml.), dried over sodium sulfate, and concentrated under vacuum to give an oil which

slowly crystallized from isopropyl ether. The crude product is recrystallized from ether-hexane to yield 104.7 g. (59%) of product; m.p. 59°—61°C.

PREPARATION G.

Ethyl 3-(3,5-dibenzyloxyphenyl)crotonate (Wittig Reaction)

A mixture of 3,5-dibenzyloxyacetophenone (43.2 g., 0.13 mole) and carbethoxymethylenetriphenylphosphorane (90.5 g., 0.26 mole) is heated under a nitrogen atmosphere at 170°C. for 4 hours. The clear melt is cooled to room temperature, triturated with ether and the precipitate of triphenyl phosphine oxide removed by filtration. The filtrate is concentrated under vacuum to an oily residue which is chromatographed over silica gel (1500 g.) and eluted with benzene:hexane solutions of increasing benzene concentration beginning with 40:60 and ending with 100% benzene. Concentration of appropriate fractions gives an oily residue which is crystallized from hexane. Yield: 40.2 g. (77%); m.p. 73°—75°C.

Analysis: Calc'd for $C_{28}H_{28}O_4$: C, 77.58; H, 6.51%
Found: C, 77.72; H, 6.60%

In like manner, ethyl 3-(3,5-dimethoxyphenyl)crotonate is prepared from 3,5-dimethoxyacetophenone (51.7 g.) and carbethoxymethylene triphenylphosphorane (200 g.). Yield = 61.8 g., 86%, b.p. 146°—162°C. at 0.3 mm.

PREPARATION H.

3-(3,5-Dibenzyloxyphenyl)-1-butanol

A solution of ethyl 3-(3,5-dibenzyloxyphenyl)crotonate (24.1 g., 60 mM) in ether (250 ml.) is added to a mixture of lithium aluminum hydride (3.42 g., 90 mM) and ether (250 ml.). Aluminum chloride (0.18 g., 1.35 mM) is added and the mixture refluxed for 12 hours and then cooled. Water (3.4 ml.), sodium hydroxide (3.4 ml. of 6N) and water (10 ml.) are then added successively to the reaction mixture. The inorganic salts which precipitate are filtered off and the filtrate is then concentrated *in vacuo* to give the desired alcohol as an oil — 2.4 g. (98%).

R_f = 0.25 [silica gel:benzene(18):ethyl acetate(1)].

m/e — 362 (m^+)

Analysis: Calc'd for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23%
Found: C, 79.37; H. 7.11%

In like manner, ethyl 3-(3,5-dimethoxyphenyl)crotonate (60.4 g.) is reduced to 3-(3,5-dimethoxyphenyl)butanol (48.0 g., 90%).

PREPARATION I.

3-(3,5-Dibenzyloxyphenyl)butyl Tosylate

Tosyl chloride (11.1 g., 58.1 mM) is added to a solution of 3-(3,5-dibenzyloxyphenyl)-1-butanol (20.7 g., 57 mM) in pyridine (90 ml.) at –45°C. The reaction mixture is held at –35°C. for 18 hours and is then diluted with cold 2N hydrochloric acid (1500 ml.) and extracted with ether (5 x 250 ml.). The combined extracts are washed with saturated sodium chloride solution (4 x 250 ml.) and then dried (Na_2SO_4). Concentration of the dried extract affords the product as an oil. It is crystallized by treatment with ether-hexane. Yield: 24.63 g. (84%).

Analysis: Calc'd for $C_{31}H_{32}O_5S$: C, 72.06; H, 6.24%
Found: C, 72.05; H, 6.29%

PREPARATION J.

3-(3,5-Dibenzyloxyphenyl)-1-phenoxybutane

A solution of phenol (4.56 g., 48.6 mM) in dimethylformamide (40 ml.) is added under a nitrogen atmosphere to a suspension of sodium hydride (2.32 g., 48.6 mM of 50% previously washed with pentane) in dimethylformamide (70 ml.) at 60°C. The reaction mixture is stirred for one hour at 60°—70°C., after which a solution of 3-(3,5-dibenzyloxyphenyl)butyl tosylate (23.93 g., 46.3 mM) in dimethylformamide (80 ml.) is added. The reaction mixture is stirred at 80°C. for a half-hour and is then cooled to room temperature, diluted with cold water (2500 ml.) and extracted with ether (4 x 400 ml.). The combined extracts are washed successively with cold 2N hydrochloric acid (2 x 300 ml.) and saturated sodium chloride solution (3 x 300 ml.) and then dried (Na_2SO_4). Removal of the solvent under reduced pressure affords

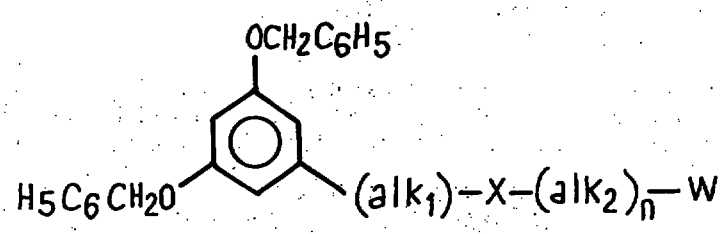
the product as an oil. The oily residue is dissolved in benzene and filtered through silica gel (100 g.). Concentration of the filtrate under reduced pressure gives the product as an oil. Yield: 14.86 g. (73%).

R_f = 0.7 (silica gel, benzene).

m/e — 438 (m^+)

Analysis: Calc'd for $C_{30}H_{30}O_3$: C, 82.16; H, 6.89%
Found: C, 82.07; H, 6.84%

Repetition of Procedures G through J, but using the 3,5-dibenzyloxy derivatives of benzaldehyde, acetophenone or propiophenone, the appropriate carbethoxy (or carbomethoxy) alkylidene triphenyl phosphorane; and the appropriate alcohol, phenol, thiophenol, hydroxypyridine or hydroxypiperidine as reactants affords the following compounds:



For convenience, the various values of W for given values of $-(alk_1)-X-(alk_2)_n-$ are collectively tabulated.

alk_1	X	alk_2	n	W
$(CH_2)_3$	O	—	0	C_6H_5, 4-FC_6H_4, C_4H_7, 4-ClC_6H_4, C_6H_{11}, 4-pyridyl, 3-pyridyl, 4-$(C_6H_5)C_6H_{10}$, 4-piperidyl, CH_3, 4-(4-FC_6H_4)C_6H_{10}.
$(CH_2)_3$	O	CH_2	1	C_6H_5, 4-FC_6H_4, C_6H_{11}, 4-piperidyl, CH_3.
$(CH_2)_3$	O	$(CH_2)_2$	1	C_6H_5, CH_3, 4-ClC_6H_4, 4-pyridyl.
$(CH_2)_3$	O	$CH(CH_3)$	1	C_6H_5, 4-FC_6H_4, CH_3, 4-piperidyl, 2-pyridyl.
$(CH_2)_3$	O	$CH(CH_3)(CH_2)_2$	1	C_6H_5, 4-pyridyl, CH_3.
$CH(CH_3)(CH_2)_2$	O	—	0	C_6H_5, 4-FC_6H_4, C_6H_{11}, C_3H_5, 4-pyridyl, C_7H_{13}, 3-piperidyl, CH_3, 4-$(C_6H_5)C_6H_{10}$, 2-(4-ClC_6H_4)C_4H_6.
$CH(CH_3)(CH_2)_2$	O	CH_2	1	C_6H_5, 4-FC_6H_4, 4-pyridyl, 2-piperidyl, CH_3.
$CH(CH_3)(CH_2)_2$	O	$(CH_2)_2$	1	C_6H_5, 4-FC_6H_4, 4-pyridyl, 4-piperidyl, CH_3, C_5H_9.
$CH(CH_3)(CH_2)_2$	O	$(CH_2)_4$	1	C_6H_5, 4-pyridyl, 2-piperidyl, CH_3, 4-$(C_6H_5)C_6H_{10}$.
$CH(CH_3)(CH_2)_2$	O	$(CH_2)_2CH(CH_3)$	1	C_6H_5, 4-FC_6H_4, CH_3, C_3H_5.
$CH(CH_3)(CH_2)_2$	O	$CH(CH_3)$		C_6H_5, 4-ClC_6H_4, CH_3, 3-piperidyl, C_7H_{13}.
$CH(CH_3)(CH_2)_2$	O	$CH_2CH(C_2H_5)$	1	C_6H_5, CH_3, C_6H_{11}.
$CH(C_2H_5)(CH_2)_2$	O	—	0	C_6H_5, 4-FC_6H_4, 2-pyridyl, CH_3, 4-piperidyl, C_3H_5, 2-(4-FC_6H_4)C_7H_{12}.
$CH(C_2H_5)(CH_2)_2$	O	$(CH_2)_2$	1	C_6H_5, 4-FC_6H_4, 4-pyridyl, C_6H_{11}, 2-piperidyl, CH_3.
$CH(C_2H_5)(CH_2)_2$	O	$(CH_2)_4$	1	C_6H_5, 4-FC_6H_4, 4-pyridyl, C_3H_5, C_5H_9.
$CH(C_2H_5)(CH_2)_2$	O	$CH(CH_3)$	1	C_6H_5, 4-FC_6H_4, CH_3, 2-pyridyl, 4-piperidyl, C_6H_{11}.
$CH(C_2H_5)(CH_2)_2$	O	$(CH_2)_2CH(CH_3)$	1	C_6H_5, 4-FC_6H_4, C_7H_{13}.
$(CH_2)_4$	O	—	0	C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-pyridyl, C_4H_7, 2-piperidyl, CH_3.
$(CH_2)_4$	O	CH_2	1	C_6H_5, 4-FC_6H_4, 4-pyridyl, 3-pyridyl, 4-piperidyl, CH_3, C_6H_{11}.
$(CH_2)_4$	O	$CH_2CH(CH_3)$	1	C_6H_5, 4-FC_6H_4, 4-$(C_6H_5)C_6H_{10}$.
$(CH_2)_4$	O	$CH(CH_3)CH_2$	1	C_6H_5, CH_3, 2-pyridyl, 3-piperidyl, 4-piperidyl, 4-FC_6H_4.

alk_1	X	alk_2	n	W
$(CH_2)_4$	O	$(CH_2)_5$	1	C_6H_5, 4-pyridyl, 3-piperidyl, 4-ClC_6H_4.
$(CH_2)_3$	S	—	0	C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-pyridyl, 2-pyridyl, 2-piperidyl, 4-piperidyl, CH_3, $C_3H_5H_9$, $C_5C_6H_{11}$, 4-$(ClC_6H_4)C_6H_{10}$.
$(CH_2)_3$	S	CH_2	1	C_6H_5, 4-FC_6H_4, CH_3, 2-pyridyl, 4-pyridyl, 3-piperidyl, C_5H_9.
$(CH_2)_3$	S	$(CH_2)_2$	1	C_6H_5, 4-ClC_6H_4, 4-pyridyl, CH_3, C_3H_5.
$(CH_2)_3$	S	$(CH_2)_4$	1	C_6H_5, 4-FC_6H_4, 4-pyridyl, CH_3, 4-piperidyl, C_6H_{11}.
$CH(CH_3)(CH_2)_2$	S	—	0	C_6H_5, 4-FC_6H_4, C_6H_{11}, CH_3, 4-pyridyl, 3-pyridyl, 4-piperidyl, C_3H_7, 4-$(C_6H_5)C_6H_{10}$.
$CH(CH_3)(CH_2)_2$	S	CH_2	1	C_6H_5, 4-FC_6H_4, CH_3, 2-pyridyl.
$CH(CH_3)(CH_2)_2$	S	$(CH_2)_2$	1	C_6H_5, 4-ClC_6H_4, CH_3, 4-pyridyl, 3-piperidyl.
$CH(CH_3)(CH_2)_2$	S	$(CH_2)_4$	1	C_6H_5, CH_3, 4-pyridyl.
$CH(C_2H_5)(CH_2)_2$	S	—	0	C_6H_5, 4-FC_6H_4, 4-$(C_6H_5)C_6H_{10}$, 4-pyridyl, 3-pyridyl, 2-piperidyl, C_6H_{11}.
$CH(C_2H_5)(CH_2)_2$	S	$CH(CH_3)$	1	C_6H_5, 4-ClC_6H_4, CH_3, 4-piperidyl.
$CH(C_2H_5)(CH_2)_2$	S	$(CH_2)_2CH(CH_3)$	1	C_6H_5, CH_3, 4-pyridyl.
$CH(CH_3)(CH_2)_3$	O	—	0	C_6H_5, CH_3, 4-FC_6H_4, 4-pyridyl, C_3H_5, C_7H_{13}, 2-(4-FC_6H_4)C_5H_8.
$CH(CH_3)(CH_2)_3$	O	$(CH_2)_2$	1	C_6H_5, CH_3, 3-pyridyl, 4-piperidyl, C_5H_{11}.
$CH(CH_3)(CH_2)_3$	S	—	0	C_6H_5, CH_3, 4-ClC_6H_4, 2-pyridyl, C_6H_{11}, 3-(4-ClC_6H_4)C_6H_{10}.
$CH(CH_3)(CH_2)_3$	S	$(CH_2)_4$	1	CH_3, C_6H_5, 4-F_6C_4, 4-pyridyl.

PREPARATION K.

3-(3,5-Dihydroxyphenyl)-1-phenoxybutane

A solution of 3-(3,5-dibenzyloxyphenyl)-1-phenoxybutane (14.7 g., 133.5 mM) in a mixture of ethyl acetate (110 ml.), ethanol (110 ml.) and concentrated hydrochloric acid (0.7 ml.) is hydrogenated for 2 hours under 60 p.s.i. hydrogen in

the presence of 10% palladium-on-carbon (1.5 g.). Removal of the catalyst by filtration and concentration of the filtrate gives an oil. The oil is purified by chromatography on silica gel (100 g.) and eluting with benzene-ethyl acetate consisting of 0—10% ethyl acetate. The middle fractions are combined and concentrated to give the title product: 7.8 g. (80%), as an oil.

R_f = 0.25 [silica gel, benzene(4), methanol(1)].

m/e – 258 (m^+)

Analysis: Calc'd for $C_{18}H_{18}O_3$: C, 74.39; H, 7.02%
Found: C, 74.13; H, 7.00%

In like manner, the remaining ethers (X = O) of Preparation J are debenzylated to afford the corresponding 3,5-dihydroxy derivatives.

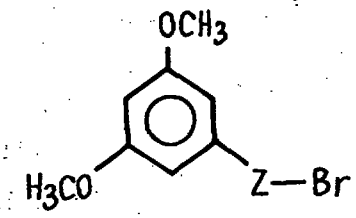
The thio ethers are debenzylated by treatment with trifluoroacetic acid. The procedure comprises stirring a solution of the dibenzyl ether (X = S) in trifluoroacetic acid at room temperature for two hours. The reaction mixture is evaporated to dryness and the residue taken up in ether. The ether solution is washed with water, dried ($MgSO_4$) and evaporated to give the debenzylated compound.

PREPARATION L.

1-Bromo-3-(3,5-dimethoxyphenyl)butane

A solution of phosphorus tribromide (5.7 ml. 0.06 mole) in ether (30 ml.) is added to a solution of 3-(3,5-dimethoxyphenyl)-1-butanol (30.0 g., 0.143 mole) in ether (20 ml.) at –5°C. to –10°C. and the reaction mixture stirred at –5°C. to –10°C. for 2.5 hours. It is then warmed to room temperature and stirred for an additional 30 minutes. The mixture is poured over ice (200 g.) and the resulting mixture extracted with ether (3 x 50 ml.). The combined extracts are washed with 5% sodium hydroxide solution (3 x 50 ml.), saturated sodium chloride solution (1 x 50 ml.) and dried (Na_2SO_4). Removal of the ether and vacuum distillation of the residue affords the title product; 25 g. (55% yield); b.p. 125°—132°C. at 0.4 mm.

The following compounds are prepared from 3,5-dimethoxybenzaldehyde, 3,5-dimethoxyacetophenone and 3,5-dimethoxypropiophenone and the appropriate carbethoxyalkylidene triphenylphosphorane by the procedures of Preparations G, H and L.



Z
$(CH_2)_3$
$(CH_2)_4$
$C(C_2H_5)CH_2$

PREPARATION M.

4-(3,5-Dihydroxyphenyl)-1-(4-pyridyl)pentane

A mixture of 3-(3,5-dimethoxyphenyl)butyl triphenylphosphonium bromide (19.0 g., 35.4 mmoles) in dimethylsulfoxide (50 ml.) is added to 4-pyridinecarboxaldehyde (3.79 g., 35.4 mmoles) in tetrahydrofuran (40 ml.). The resulting mixture is then added dropwise to a slurry of 50% sodium hydride (1.87 g., 39 mmoles) in tetrahydrofuran (20 ml.) under a nitrogen atmosphere at 0°—5°C. Following completion of addition, the mixture is stirred for one hour at 0°—5°C. and then concentrated under reduced pressure. The concentrate is diluted with water (200 ml.) and then acidified with 6N HCl. The aqueous acid solution is extracted with benzene (4 x 50 ml.). It is then made basic and extracted with ethyl

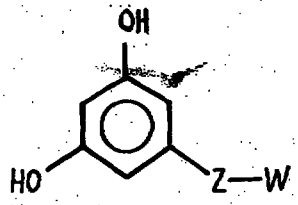
acetate (3 x 50 ml.). Evaporation of the combined extracts after drying ($MgSO_4$) affords 4-(3,5-dimethoxyphenyl)-1-(4-pyridyl)-1-pentene (7.1 g., 70%) as an oil.

Catalytic hydrogenation of the thus-produced pentene derivative according to the procedure given in Preparation D gives 4-(3,5-dimethoxyphenyl)-1-(4-pyridyl)-pentane in quantitative yield; m.p. 131°—133°C.

The pentane derivative thus obtained is demethylated by heating a mixture of the compound (7.15 g., 25 mmoles) and pyridine hydrochloride (35 g.) under a nitrogen atmosphere at 210°C. for 8 hours. The hot mixture is poured into water (40 ml.) and the resulting solution made basic with 6N sodium hydroxide. Water and pyridine are removed by distillation *in vacuo*. Ethanol (50 ml.) is added to the residue and the inorganic salts which precipitate are filtered off. The filtrate is concentrated *in vacuo* and the residue chromatographed on silica gel (150 g.) using an eluting agents 5% ethanol/benzene (4 liters), 10% ethanol/benzene (1 liter), 13% ethanol/benzene (1 liter) and 16% ethanol-benzene (5 liters). The product is isolated as a glassy solid by concentration of appropriate fractions of the eluate. Yield = 5.0 g (78%).

The 3-(3,5-dimethoxyphenyl)butyltriphenylphosphonium bromide is prepared by refluxing a mixture of 1-bromo-3-(3,5-dimethoxyphenyl)butane (21.5 g., 78.5 mmoles) and triphenyl phosphine (20.5 g., 78.5 mmoles) in xylene (60 ml.) for 18 hours. The reaction mixture is then cooled to room temperature and filtered. The filter cake is washed with ether and dried in a vacuum desicator to give 36.4 g. (86%) yield of product; m.p. 190°—200°C.

Repetition of this procedure but using the appropriate bromo-(3,5-dimethoxyphenyl)alkane and the appropriate aldehyde or ketone affords the following compounds.



Z	W
$(CH_2)_3$	2-pyridyl
$(CH_2)_3$	3-pyridyl
$(CH_2)_3$	4-pyridyl
$(CH_2)_3$	2-piperidyl
$(CH_2)_3$	4-piperidyl
$(CH_2)_4$	2-pyridyl
$(CH_2)_4$	4-pyridyl
$(CH_2)_4$	3-piperidyl
$(CH_2)_4$	4-piperidyl
$CH_2CH(CH_3)CH_2$	2-pyridyl
$CH_2CH(CH_3)CH_2$	4-piperidyl
$CH(CH_3)CH(CH_3)CH_2$	3-pyridyl
$CH(CH_3)CH(CH_3)CH_2$	4-pyridyl
$CH(CH_3)CH(CH_3)CH_2$	3-piperidyl

Z	W
$CH(CH_3)(CH_2)_2$	2-pyridyl
$CH(CH_3)(CH_2)_2$	3-pyridyl
$CH(CH_3)(CH_2)_2$	4-piperidyl
$CH(CH_3)(CH_2)_3$	3-pyridyl
$CH(CH_3)(CH_2)_3$	4-piperidyl
$CH(CH_3)CH(C_2H_5)CH_2$	4-pyridyl
$CH(C_2H_5)(CH_2)_2$	4-pyridyl
$CH(C_2H_5)(CH_2)_2$	2-piperidyl
$CH(C_2H_5)(CH_2)_2$	4-piperidyl
$CH_2CH(C_2H_5)CH_2$	3-pyridyl
$CH(C_2H_5)(CH_2)_3$	3-pyridyl
$CH(C_2H_5)(CH_2)_3$	4-piperidyl
$CH(C_2H_5)CH(CH_3)CH_2$	2-pyridyl
$CH(C_2H_5)CH(C_2H_5)CH_2$	4-pyridyl
$CH(C_2H_5)CH(C_2H_5)CH_2$	2-piperidyl
$(CH_2)_3$	C_6H_{11}
$CH(CH_3)(CH_2)_3$	C_6H_{11}
$(CH_2)_4$	C_3H_5
$(CH_2)_2$	C_4H_7
$CH_2CH(CH_3)CH_2$	C_5H_9
$CH(CH_3)(CH_2)_2$	C_7H_{13}
$CH(CH_3)CH(CH_3)CH_2$	C_6H_{11}
$(CH_2)_6$	C_6H_5
$(CH_2)_7$	C_6H_5
$(CH_2)_8$	C_6H_5
$CH(CH_3)(CH_2)_6$	C_6H_5
$CH(CH_3)(CH_2)_7$	C_6H_5
$CH(CH_3)(CH_2)_3$	$4\text{-}FC_6H_4$
$C(CH_3)_2(CH_2)_3$	C_6H_5
$CH(CH_3)(CH_2)_3$	$4\text{-}ClC_6H_4$
$CH(CH_3)(CH_2)_4$	$4\text{-}ClC_6H_4$
$CH(CH_3)(CH_2)$	$4\text{-}ClC_6H_4$

Z	W
$CH(CH_3)(CH_2)$	$4\text{-}FC_6H_4$
$CH(CH_3)(CH_2)_2$	$4\text{-}FC_6H_4$
$CH(CH_3)(CH_2)_2$	$4\text{-}ClC_6H_4$
$(CH_2)_3CH(CH_3)$	C_6H_{11}
$CH(CH_3)(CH_2)_2CH(CH_3)$	C_6H_5
$CH(CH_3)(CH_2)_2CH(CH_3)$	C_6H_{11}
$CH(CH_3)(CH_2)_2CH(CH_3)$	4-piperidyl
$CH(CH_3)(CH_2)_3$	C_6H_{11}
$CH(CH_3)(CH_2)_2CH(CH_3)$	C_6H_{11}
$(CH_2)_3$	C_6H_{11}
$(CH_2)_4$	C_6H_{11}
$(CH_2)_5$	C_6H_{11}

PREPARATION N.

3,5-Dimethoxy-α-methylstyrene Oxide

To a solution of dimethylsulfoxonium methylide (69.4 mM) in dimethylsulfoxide (65 ml.) at room temperature is added solid 3,5-dimethoxyacetophenone (10 g., 55.5 mM). The reaction mixture is stirred for one hour at 25°C., for one-half hour at 50°C. and is then cooled. The mixture is diluted with water (50 ml.) and added to a mixture of ice water (200 ml.) — ether (250 ml.) — low boiling petroleum ether (25 ml.). The organic extract is washed twice with water (250 ml.), dried ($MgSO_4$) and evaporated to an oil. Fractional distillation of the oil yields 8.0 g. (75%) of 3,5-dimethoxy-α-methylstyrene oxide, b.p. 93°—97°C., 0.2 mm.

IR (CCl_4): 2780, 1595, 1196, 1151, 1058 cm^{-1}.
UV (95% ethanol): λ_{max} = 279 nm (ϵ = 2068).
m/e – 194 (m^+)
PMR ($CDCl_3$) (60 MHz): δ 1.70 (S,CH_3—), 2.76 (d,J = 6 Hz, ), 2.95 (d,J = 6Hz, ), 3.81 (S,CH_3O—), 6.41 (t,J = 2Hz, ArH) and 6.58 (d,J = 2Hz, ArH).

Analysis: Calc'd for $C_{11}H_{14}O_3$:C, 68.02; H, 7.27%
Found:C, 67.96; H, 7.28%

PREPARATION O.

2-(3,5-Dimethoxyphenyl)-2-hydroxypropyl-2-phenylethyl Ether

A mixture of dry 2-phenylethanol (30 ml., 251 mM) and sodium metal (690 mg., 30 mM) is heated at 110°C. for 30 minutes. The resulting 1M solution of sodium 2-phenylethoxide is cooled to 60°C., 3,5-dimethoxy-α-methylstyrene oxide (2 g., 10.3 mM) added and the reaction heated 15 hours at 60°C. The reaction mixture is cooled and added to a mixture of ether and water. The ether extract is dried over magnesium sulfate and evaporated. Excess 2-phenylethanol is removed by vacuum distillation (b.p. ~65°C., 0.1 mm.) leaving a 3.5 g. residue. The residue is purified via column chromatography on Merck silica gel 60 (300 g.) and eluted in 15 ml. fractions with 60% ether-pentane. Fractions 52—88 yielded 2.9 g. (89%) of 2-(3,5-dimethoxyphenyl)-2-hydroxypropyl 2-phenylethyl ether.

IR (CCl_4): 3534, 1595, 1202, 1153 cm^{-1}.
UV (95% ethanol): λ_{max} = 278 (ϵ = 1830), 273 (ϵ = 1860).

m/e – 316 (m^+)

PMR ($CDCl_3$, 60 MHz): δ 1.46 (S,CH_3—), 2.86 (S,OH), 2.86 (t,J = 7Hz, —CH_2—Ph), 3.53 (S,—CH_2O), 3.71 (t,J = 7Hz,—CH_2O), 3.80 (S,OCH_3), 6.38 (t,J = 2Hz, ArH), 6.61 (d,J = 2Hz, ArH) and 7.23 (S,PhH).

Analysis: Calc'd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65%
Found: C, 71.92; H, 7.63%

PREPARATION P.

2-(3,5-Dimethoxyphenyl)propyl 2-Phenylethyl Ether

To a 0°C. solution of 2-(3,5-dimethoxyphenyl)-2-hydroxypropyl 2-phenylethyl ether (550 mg., 1.74 mM) in pyridine (2 ml.) is added dropwise phosphorous oxychloride (477 ml. 5.22 mM). The reaction is allowed to warm to 20°C. over a 1.5 hour period. It is then stirred for 1.5 hours at 20°C. and then added to ether (150 ml.) and 15% sodium carbonate (100 ml.). The organic phase is separated and washed with 15% sodium carbonate (3 x 50 ml.), dried over magnesium sulfate and evaporated to an oil. The oil is dissolved in absolute ethanol (15 ml.), 10% palladium-on-carbon (100 mg.) added and the mixture stirred under one atmosphere of hydrogen gas. When hydrogen uptake ceases (26.5 ml., 20 min.), the reaction is filtered through diatomaceous earth and the filtrate evaporated to an oil. The oil is purified via preparative layer chromatography on silica gel plates, eluted twice with 6:1 pentane:ether to yield 211 mg. (40%) of 2-(3,5-dimethoxyphenyl)propyl 2-phenylethyl ether.

IR (CCl_4): 1600, 1205, 1155, 1109 cm^{-1}.

m/e – 300 (m^+)

PMR ($CDCl_3$, 60 MHz) δ 1.22 (d,J = 7Hz, CH_3—), 2.82 (t,J = 7Hz, CH_2Ph), ~2.8 (H—C—Me), ~3.6 (—CH_2—O—CH_2—), 3.75 (S,OCH_3), 6.35 (m,ArH) and 7.18 (S,PhH).

PREPARATION Q.

2-(3,5-Dihydroxyphenyl)propyl 2-Phenylethyl Ether

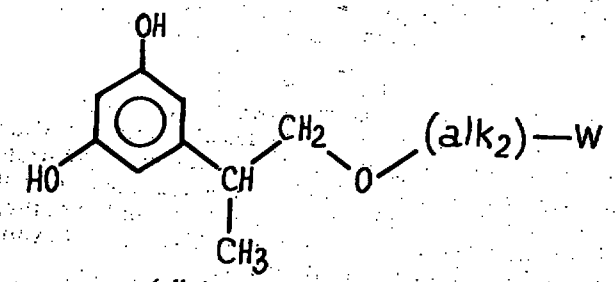
A mixture of 2-(3,5-dimethoxyphenyl)propyl 2-phenylethyl ether (195 mg., 0.65 mM), pyridine (0.4 ml., 4.96 mM) and dry pyridine hydrochloride (4 g., 34.6 mM) is heated at 190°C. for 6 hours. The reaction mixture is cooled and added to a mixture of water (100 ml.) and ether (150 ml.). The ether extract is washed once with water (50 ml.) and, along with a second ether extract (50 ml.) of the aqueous phase, is dried over magnesium sulfate and evaporated to an oil. The oil is purified via preparative layer chromatography on silica gel plates, eluted six times with 30% ether-pentane to yield 65.8 mg. (37%) of 2-(3,5-dihydroxyphenyl)propyl 2-phenylethyl ether.

IR ($CHCl_3$): 3559, 3279, 1605, 1147, 1105 cm^{-1}.

m/e – 272 (m^+)

PMR ($CDCl_3$, 60 MHz) δ 1.18 (d,J = 7Hz, CH_3—), 2.80 (t,J = 7Hz, —CH_2Ph), 2.80 (H—C—Me), 3.4—3.8 (—CH_2OCH_2—), 6.08 (t,J = 2Hz, ArH), 6.21 (d,J = 2Hz, ArH) and 7.16 (S,PhH).

The following compounds are prepared from appropriate alkanols by the methods of Procedures O and P.



(alk_2)	W
—$(CH_2)_6$—	CH_3
—$(CH_2)_6$—	C_6H_5
—$(CH_2)_4$—	CH_3

(alk_2)	W
$—CH(CH_3)CH_2—$	CH_3
$—CH(CH_3)(CH_2)_4—$	CH_3
$—(CH_2)—$	$4\text{-}FC_6H_4$
$—(CH_2)_2—$	4-pyridyl
$—(CH_2)_2—$	2-piperidyl
$—CH(CH_3)CH_2—$	4-piperidyl
$—(CH_2)_2CH(CH_3)(CH_2)_2—$	CH_3
$—CH(CH_3)—$	CH_3
$—C(CH_3)_2—$	CH_3

PREPARATION R.

4-(3,5-Dihydroxyphenyl)-1-phenoxypentane.

Under a nitrogen atmosphere a mixture of 3,5-dibenzyloxyacetophenone (50.0 g., 0.15 M) in tetrahydrofuran (175 ml.) and 3-phenoxypropyltriphenylphosphonium bromide (7.18 g., 0.15 M) in dimethylsulfoxide (450 ml.) is added dropwise over 1.75 hours to a suspension of 50% sodium hydride (7.89 g., 0.165 M) (previously washed with pentane) in tetrahydrofuran (75 ml.) maintained at 0°—5°C. After stirring for 4 hours at 0°—5°C. the reaction is allowed to warm to room temperature and is then carefully stirred into ice water (2000 ml.), acidified with concentrated hydrochloric acid, and extracted with ethyl acetate (5 x 400 ml.). The combined organic phases are washed with saturated sodium chloride solution (3 x 300 ml.), dried over sodium sulfate and concentrated under vacuum to yield an oil which is triturated with ether to precipitate triphenylphosphine oxide. Filtration, followed by concentration of the filtrate, gives an oily residue which is chromatographed over silica gel (1300 g.) eluting with benzene-hexane consisting of 30% to 100% benzene. From the middle fractions 51 g. (75%) of 4-(3,5-dibenzyloxyphenyl)-1-phenoxypent-3-ene is isolated as an oil; $R_f = 0.8$ (silica gel, 2-benzene:1-hexane); m/e — 450 (m^+).

Analysis: Calc'd for $C_{31}H_{30}O_3$: C, 82.63; H, 6.71%
Found: C, 82.90; H, 6.69%

A solution of 4-(3,5-dibenzyloxyphenyl)-1-phenoxypent-3-ene (51 g., 0.113 M) in a mixture of absolute ethanol (160 ml.), ethyl acetate (160 ml.) and concentrated hydrochloric acid (0.2 ml.) is hydrogenated for 12 hours under 55 lbs. hydrogen in the presence of 10% Pd/C. Removal of the catalyst by filtration and concentration of the filtrate under vacuum yields 30.8 g. (100%) of product as a viscous oil.

Analysis: Calc'd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40%
Found: C, 74.54; H, 7.45%

PREPARATION S.

3,5-Dimethoxy-β-methylstyrene oxide.

To a −78°C. solution of diphenylsulfonium ethylide (1.0 mole) in tetrahydrofuran (one liter) is slowly added 3,5-dimethoxybenzaldehyde (1.0 mole). The reaction mixture is stirred at −78°C. for 3 hours and then allowed to warm to room temperature. It is then added to ether-water and the ether phase separated. The ether phase is washed with water, dried ($MgSO_4$) and evaporated. Fractional distillation of the residue gives the title product.

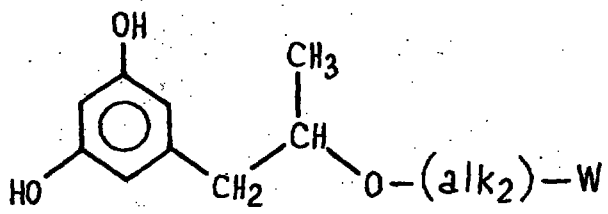
PREPARATION T.

3-(3,5-Dihydroxyphenyl)-2-propylbutyl Ether.

To a solution of sodium butoxide in butanol (0.5 liters of 1M) is added 3,5-dimethoxy-β-methylstyrene oxide (6.33 M). The mixture is heated for 18 hours at 70°C. and is then cooled and added to a mixture of ether-water. The ether solution is separated, dried ($MgSO_4$) and evaporated to give 3-(3,5-dimethoxyphenyl)-3-

hydroxy-2-propyl butyl ether. It is purified by column chromatography on silica gel with ether-pentane elution.

By means of the procedure of Preparation P the title product is produced. Similarly, the following are prepared from appropriate alcohols.



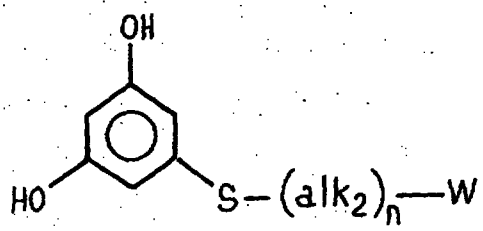
(alk_2)	W
CH_2	CH_3
$(CH_2)_6$	CH_3
$(CH_2)_3$	C_6H_5
$(CH_2)_2$	4-FC_6H_4
$(CH_2)_2$	4-pyridyl
$CH(CH_3)CH_2$	CH_3
$CH(C_2H_5)—(CH_2)_2$	CH_3
$CH(CH_3)CH_2$	C_6H_5

PREPARATION U.

Alkylation of 3,5-Dihydroxyphenylmercaptan.

A solution of 3,5-dihydroxyphenylmercaptan (3.5 g., 0.01 mole) in absolute ethanol (50 ml.) is made just alkaline with sodium ethoxide. The appropriate bromide of formula $Br—(alk_2)_n—W$ (0.01 mole) is added and the mixture refluxed for 3 hours. It is then concentrated under reduced pressure and the residue extracted with ether. Evaporation of the ether affords the product.

The following compounds are thus prepared:



n	(alk_2)	W
1	$—CH(CH_3)(CH_2)_5—$	CH_3
1	$—CH(CH_3)CH(CH_3)(CH_2)_4—$	CH_3
1	$—C(CH_3)_2(CH_2)_5—$	CH_3
1	$—(CH_2)_6—$	CH_3
1	$—(CH_2)_4—$	CH_3
1	$—CH_2—$	C_6H_5

n	(alk$_2$)	W
1	—$(CH_2)_2$—	C_6H_5
1	—$CH(CH_3)(CH_2)_3$—	C_6H_5
1	—CH_2—	C_3H_5
1	—CH_2—	C_5H_9
1	—CH_2—	C_6H_{11}
1	—$(CH_2)_2$—	C_5H_9
1	—$(CH_2)_3$—	C_5H_9
1	—$(CH_2)_5$—	C_6H_{11}
1	—$(CH_2)_4$—	C_5H_9
1	—$(CH_2)_3CH(C_2H_5)$—	C_6H_{11}
1	—$(CH_2)_7$—	C_5H_9
1	—$(CH_2)_4$—	C_7H_{13}
1	—$(CH_2)_2$—	C_7H_{13}
1	—$(CH_2)_5$—	C_4H_7
1	—$(CH_2)_5$—	C_3H_5
1	—(CH_2)—	2-piperidyl
1	—$(CH_2)_3$—	4-piperidyl
1	—(CH_2)—	2-pyridyl
1	—$(CH_2)_3$—	3-pyridyl
1	—$(CH_2)_4$—	2-pyridyl
1	—$CH(CH_3)(CH_2)_2$—	2-pyridyl
1	—$CH(CH_3)(CH_2)_3$—	4-pyridyl
1	—$CH(C_2H_5)(CH_2)_2$—	4-piperidyl
1	—$(CH_2)_4$—	4-FC_6H_4
1	—$CH(CH_3)(CH_2)_2$—	4-ClC_6H_4
1	—$CH(CH_3)(CH_2)_3$—	4-FC_6H_4
0	—	C_6H_5
0	—	4-FC_6H_4
0	—	4-ClC_6H_4
0	—	C_3H_5
0	—	C_5H_9
0	—	C_6H_{11}

n	(alk_2)	W
0	—	C_7H_{13}
0	—	4-pyridyl
0	—	2-piperidyl
0	—	2-pyridyl
0	—	2-(C_6H_5)C_3H_4
0	—	4-(C_6H_5)C_6H_{10}
0	—	3-(C_6H_5)C_7H_{12}
0	—	CH_3

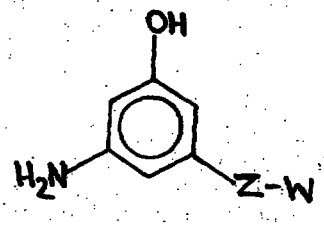
PREPARATION V.

3-Hydroxy-5-pentylaniline.

Olivetol (1.8 g., 0.01M), ammonium chloride (2.65 g., 0.05M), sodium bisulfite (5.2 g., 0.05M) and ammonium hydroxide (12.5 ml.) are combined and heated in a steel bomb at 230°C. for a half-hour. The bomb is then cooled; the contents dissolved in ethyl acetate (350 ml.). Hydrochloric acid (300 ml. of 10%) is added, the mixture stirred and then the organic layer separated. The extraction is repeated two more times. The aqueous acid solution is neutralized with 6N sodium hydroxide and then extracted with chloroform (3 x 300 ml.). The combined chloroform extracts are dried and concentrated. The residue is taken up in ethyl acetate, decolorized with charcoal and concentrated. The addition of hexane to the residue causes it to crystallize: 270 mg.; m.p. 88°—91°C. When recrystallized from hot ethyl acetate-hexane (1—1) it melts at 95°—96°C.

Analysis: Calc'd for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81%
Found: C, 73.64; H, 9.62; N, 7.91%

In like manner, the compounds of Preparations C, D, E, K, M, Q, R, T, U and CC are converted to the corresponding aniline derivatives having the formula



wherein Z and W are as defined in said Preparations.

PREPARATION W.

d,l-N-Acetyl-3-hydroxy-5-(5-phenyl-2-pentyl)aniline.

A solution of 2.4 g. (9.5 mmole) *d,l*-3-hydroxy-5-(5-phenyl-2-pentyl)aniline in 24 ml. pyridine and 24 ml. acetic anhydride is stirred at room temperature for 45 minutes. The reaction mixture is poured onto 200 ml. each of water and ethyl acetate. After stirring for 10 minutes, the organic layer is separated and washed successively with water (4 x 100 ml.), brine (1 x 100 ml.), dried ($MgSO_4$), filtered and concentrated to yield 3.5 g. of crude *d,l*-N-acetyl-3-acetoxy-5-(5-phenyl-2-pentyl)aniline. A solution of *d,l*-N-acetyl-3-acetoxy-5-(5-phenyl-2-pentyl)aniline and 1 g. potassium carbonate in 100 ml. methanol is stirred at room temperature for one hour, filtered, concentrated and dissolved in ethyl acetate. The organic solution is washed with water, dried ($MgSO_4$) and concentrated to an oil which is crystallized from hexane to yield 1.5 g. *d,l*-N-acetyl-3-hydroxy-5-(5-phenyl-2-pentyl)aniline, m.p. 128°—130°C.

m/e — 297 (m^+)

^{1}H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 8.64 (bs, 1H, —NH), 7.12, 6.58 and 6.45 (bs, 1H variable, ArOH), 2.18—2.78 (m, 3H, Ar—CH and Ar—CH_2), 2.05 (s, 3H, CH_3—C(=O)—), 1.3—1.78 (m, 4H, $(CH_2)_2$), 1.12 (d, 3H, —C—CH_3).

PREPARATION X.

d,l-3-Benzyloxy-5-(5-phenyl-2-pentyl)aniline.

To a stirred solution of 1.2 g *d,l*-N-acetyl-3-hydroxy-5-(5-phenyl-2-pentyl)aniline (4.03 mmole) in 50 ml. tetrahydrofuran is added 193 mg. of 50% sodium hydride (4.03 mmole). After 30 minutes of stirring, 1.38 g. (8.06 mmole) of α-bromotoluene is added and stirring continued for 16 hours. The reaction mixture is then filtered, 1 ml. of acetic acid added to the filtrate which is then concentrated and chromatographed (silica gel, benzene/ether [2:1] as eluant) to yield 1.43 g. *d,l*-N-acetyl-3-benzyloxy-5-(5-phenyl-2-pentyl)aniline as an oil.

m/e — 387 (m^+)

^{1}H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 7.88 (bs, 1H, N—H), 7.38, 7.20, 6.84, 6.59 (bs, 5H, 6H, 1H, 1H, aromatic), 5.0 (s, 2H, —O—CH_2Ar), 2.21—2.98 (m, 3H,) Ar—CH and Ar—CH_2), 2.07 (s, 3H, CH_3—C(=O)—N), 1.30—1.69 (m, 4H, —$(CH_2)_2$), 1.15 (d, 3H, CH_3—$\underset{|}{C}$—Ar).

A solution of 1.4 g. *d,l*-N-acetyl-3-benzyloxy-5-(5-phenyl-2-pentyl)aniline, 14 ml. 20% potassium hydroxide, 14 ml. methanol and 10 ml. 2-propanol is heated at reflux on a steam bath for 4 days. After cooling, water and ethyl acetate are added and the mixture stirred for 10 minutes. The organic phase is separated and the aqueous phase extracted again with ethyl acetate. The organic solutions are combined, dried ($MgSO_4$), concentrated *in vacuo* and chromatographed (35 g. silica gel, benzene/ether [3:1] as eluent) to yield *d,l*-3-benzyloxy-5-(5-phenyl-2-pentyl)-aniline as an oil.

m/e — 345 (m^+)

^{1}H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 7.32 (bs, 5H, aromatic), 7.13 (bs, 5H, aromatic), 6.01—6.33 (m, 3H, aromatic), 4.95 (s, 2H, $ArCH_2O$), 3.48 (bs, 2H variable, NH_2), 2.17—2.88 (m, 3H, Ar—CH and Ar—CH_2), 1.32—1.76 (m, 4H, $(CH_2)_2$), 1.14 (d, 3H, —C—CH_3).

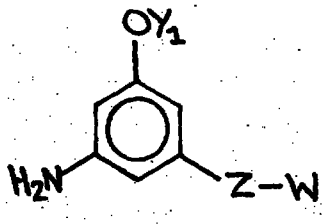
Following the procedures of Preparations W and X, the 3-hydroxy-5-(Z—W)-anilines of Preparation V are converted to 3-benzyloxy-5-(Z—W)anilines wherein Z and W are as defined in Preparation V.

PREPARATION Y.

d,l-3-Methoxy-5-(5-phenyl-2-pentyl)aniline.

The procedures of Preparations W and X are repeated but using methyl bromide in place of α-bromotoluene to give the title product.

Similarly, the compounds of Preparation V are reacted with methyl bromide or ethyl bromide to give compounds having the formula



wherein Z and W are as defined in Preparation V and Y_1 is methyl or ethyl.

PREPARATION Z.

3,5-Diethoxyaniline.

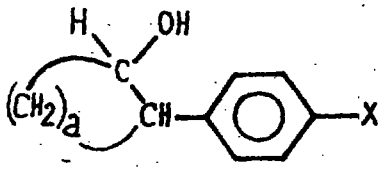
A mixture of 3-ethoxy-5-hydroxynitrobenzene (8.7 g.), diethyl sulfate (9.1 g.), potassium carbonate (7.4 g.) and toluene (200 ml.) is heated at reflux for four hours. The toluene is removed by steam distillation and the residue cooled. The solid product 3,5-diethoxy nitrobenzene is recovered by filtration and dried.

The solid (11 g.) is dissolved in glacial acetic acid (100 ml.) and water (100 ml.). Tin (1 g.) is added, followed by a solution of stannous chloride (7 g.) in concentrated hydrochloric acid (70 ml.). The mixture is stirred vigorously and held at 40°C. for six hours. It is then made alkaline with sodium hydroxide and extracted with ether (3 x 100 ml.). The combined extracts are dried (Na_2SO_4) and evaporated to give the product. It is purified by vacuum distillation.

PREPARATION AA.

(2-Halophenyl)cycloalkanols.

The procedure of Huitric *et al., J. Org. Chem., 23,* 715—9 (1962) is employed but using the appropriate cycloalkylene oxide and p-halo (Cl or F) phenyl lithium reactants to produce the following compounds.



a	X	a	X
2	Cl	2	F
3	Cl	3	F
5	Cl	5	F

PREPARATION BB.

(4-Halophenyl)cyclohexanols.

A. *3- and 4-(4-Fluorophenyl)cyclohexanols.*

A benzene solution containing equimolar amounts of 4-fluorostyrene and 2-methoxybutadiene and hydroquinone (1% by weight based on diene) is heated in a sealed tube at 150°C. for 10 hours. The reaction vessel is cooled, the contents removed and concentrated to give 1-methoxy-4(and 5)-4-(fluorophenyl)cyclohexene which are separated by distillation *in vacuo*. Hydrolysis of the ether with 3% hydrochloric acid affords 3- and 4-(4-fluorophenyl)cyclohexanones.

Sodium borohydride reduction of the ketones according to the procedure of Example 31 affords the hydroxy compounds.

In like manner, the corresponding 3- and 4-(4-chlorophenyl)cyclohexanols are prepared from 4-chlorostyrene.

B. *2-(4-Fluorophenyl)cyclohexanol.*

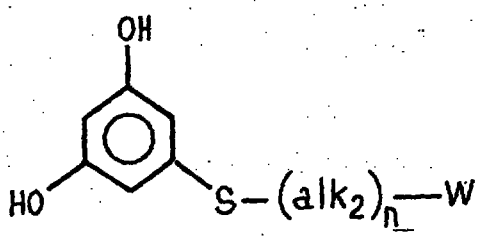
This compound is prepared from cyclohexane oxide and p-fluorophenyl lithium according to the procedure of Huitric *et al., J. Org. Chem., 27,* 715—9 (1962), for preparing 2-(4-chlorophenyl)cyclohexanol.

PREPARATION CC.

Alkylation of 3,5-Dihydroxyphenylmercaptan.

A solution of 3,5-dihydroxyphenylmercaptan (3.5 g., 0.01 mole) in absolute ethanol (50 ml.) is made just alkaline with sodium ethoxide. The appropriate bromide of formula Br—$(alk_2)_n$—W (0.01 mole) is added and the mixture refluxed for 3 hours. It is then concentrated under reduced pressure and the residue extracted with ether. Evaporation of the ether affords the product.

The following compounds are thus prepared:



n	(alk_2)	W
1	—$CH(CH_3)(CH_2)_6$—	H
1	—$CH(CH_3)CH(CH_3)(CH_2)_4$—	CH_3
1	—$C(CH_3)_2(CH_2)_6$—	CH_3
1	—$(CH_2)_8$—	CH_3
1	—$(CH_2)_4$—	CH_3
1	—CH_2—	C_6H_5
1	—$(CH_2)_2$—	C_6H_5
1	—$CH(CH_3)(CH_2)_3$—	C_6H_5
1	—CH_2—	C_3H_5
1	—CH_2—	C_5H_9
1	—CH_2—	C_6H_{11}
1	—$(CH_2)_2$—	C_5H_9
1	—$(CH_2)_5$—	C_6H_{11}
1	—$(CH_2)_4$—	C_5H_9
1	—$(CH_2)_3CH(C_2H_5)$—	C_6H_{11}
1	—$(CH_2)_7$—	C_5H_9
1	—$(CH_2)_4$—	C_7H_{13}
1	—$(CH_2)_2$—	C_7H_{13}
1	—$(CH_2)_5$—	C_4H_7
1	—$(CH_2)_5$—	C_3H_5
1	—(CH_2)—	2-piperidyl
1	—$(CH_2)_3$—	4-piperidyl
1	—(CH_2)—	2-pyridyl
1	—$(CH_2)_3$—	3-pyridyl
1	—$(CH_2)_4$	2-pyridyl
1	—$CH(CH_3)(CH_2)_2$—	2-pyridyl
1	—$CH(CH_3)(CH_2)_3$—	4-pyridyl
1	—$CH(C_2H_5)(CH_2)_2$—	4-piperidyl
1	—$(CH_2)_4$—	4-FC_6H_4
1	—$CH(CH_3)(CH_2)_2$—	4-ClC_6H_4
1	—$CH(CH_3)(CH_2)_3$—	4-FC_6H_4

n	(alk_2)	W
0	—	C_6H_5
0	—	4-FC_6H_4
0	—	4-ClC_6H_4
0	—	C_3H_5
0	—	C_5H_9
0	—	C_6H_{11}
0	—	C_7H_{13}
0	—	4-pyridyl
0	—	2-piperidyl
0	—	2-pyridyl
0	—	2-(C_6H_5)C_3H_4
0	—	4-(C_6H_5)C_6H_{10}
0	—	3-(C_6H_5)C_7H_{12}
0	—	CH_3

PREPARATION DD.

d,l-5-Phenyl-2-Pentanol Mesylate.

To a stirred solution of 5-phenyl-2-pentanol (482 g.; 2.94 moles) in tetrahydrofuran (2250 ml.) at 0°C. is added methanesulfonyl chloride (300 ml.) at such a rate that the internal temperature does not rise above 10°C. (total addition time 4.5 hours). After addition is complete, the reaction mixture is allowed to warm to room temperature and stirring is continued for an additional hour. The reaction mixture is filtered and the supernate concentrated to a light yellow oil (2800 g.) which is dissolved in chloroform (2 l.) and washed with water (4 × 1 l.), brine (1 × 1 l.), charcoal treated (50 g.) dried ($MgSO_4$), filtered through diatomaceous earth and concentrated to a light orange oil (687 g., 95% yield). This material is suitable for use without further purification.

^{1}H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 7.23 (s, 5H, aromatic), 4.53—5.13 (m, 1H, —CH—O—), 2.93 (s, 3H, O—SO_2—CH_3), 2.42—2.93 (m, 2H, —$CH_2C_6H_5$), 1.50—1.92 (m, 4H, —$(CH_2)_2$—), 1.23 (s, 3H, O—CH—CH_3).

Similarly, the following mesylates are prepared from appropriate alcohols:

4-phenylbutanol mesylate, a yellow oil.

m/e — 228 (m^+)

^{1}H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 7.22 (bs, 5H, aromatic), 4.08—4.34 (m, 2H, —CH_2—O—), 3.93 (s, 3H, SO_2CH_3), 2.40—2.82 (m, 2H, —$CH_2C_6H_5$), 1.51—1.93 (m, 4H, —$(CH_2)_2$—).

l-2-octanol mesylate, a colorless oil.

$[\alpha]_D^{25} = -9.695°$ (C — 2.6, $CHCl_3$)

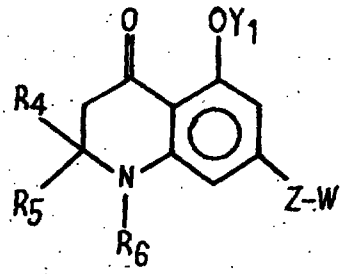
^{1}H NMR (60 MHz) $\delta^{TMS}_{CDCl_3}$ (ppm): 4.79 (bg, 1H, —CH—O—), 2.97 (s, 3H, S—CH_3), 1.40 (d, 3H, CH_3—CH), 0.87 (t, 3H, CH_3—CH_2), 1.0—2.0 (m, 10 H, —$(CH_2)_5$—).

d-2-octanol mesylate.

$[\alpha]_D^{28} = +9.238°$ (C = 2.8, $CHCl_3$)
^1H NMR, identical to the l-form.

WHAT WE CLAIM IS:—

1. A compound having the formula:



wherein

Y_1 is selected from hydrogen, benzyl, methyl and ethyl;

R_4 is selected from hydrogen, alkyl having from 1 to 6 carbon atoms and $-(CH_2)_z-C_6H_5$ wherein z is an integer from 1 to 4;

R_5 is selected from hydrogen, methyl and ethyl;

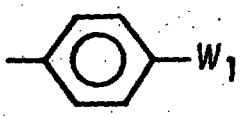
R_6 is selected from hydrogen, $-(CH_2)_y-$ carbalkoxy having from one to four carbon atoms in the alkoxy group and wherein y is 0 or an integer from 1 to 4, carbobenzyloxy, formyl, alkanoyl having from two to five carbon atoms, alkyl having from one to six carbon atoms and $-(CH_2)_x-C_6H_5$; and $-CO(CH_2)_{x-1}-C_6H_5$; wherein x is an integer from 1 to 4;

Z is selected from

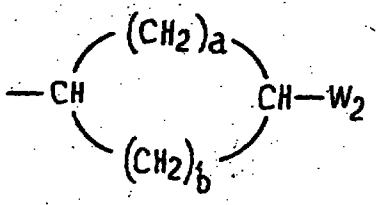
(a) alkylene having from one to nine carbon atoms;

(b) $-(alk_1)_m-X-(alk_2)_n-$ wherein each of (alk_1) and (alk_2) is alkylene having from one to nine carbon atoms, with the proviso that the summation of carbon atoms in (alk_1) plus (alk_2) is not greater than nine; each of m and n is 0 or 1; X is selected from the group consisting of 0, S, SO and SO_2; and

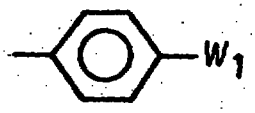
W is selected from hydrogen, methyl, pyridyl, piperidyl,



wherein W_1 is selected from hydrogen, fluoro and chloro; and



wherein W_2 is selected from hydrogen and

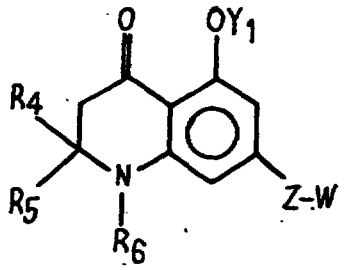


a is an integer from 1 to 5 and b is 0 or an integer from 1 to 5; with the proviso that the sum of a and b is not greater than 5.

$[\alpha]_D^{28} = +9.238°$ (C = 2.8, $CHCl_3$)
^1H NMR, identical to the l-form.

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1. A compound having the formula:



wherein

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R_5 is selected from hydrogen, methyl and ethyl;

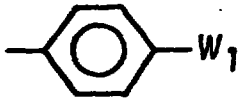
R_6 is selected from hydrogen, $-(CH_2)_y-$ carbalkoxy having from one to four carbon atoms in the alkoxy group and wherein y is 0 or an integer from 1 to 4, carbobenzyloxy, formyl, alkanoyl having from two to five carbon atoms, alkyl having from one to six carbon atoms and $-(CH_2)_x-C_6H_5$; and $-CO(CH_2)_{x-1}-C_6H_5$; wherein x is an integer from 1 to 4;

Z is selected from

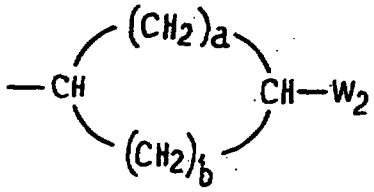
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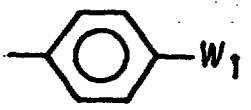
W is selected from hydrogen, methyl, pyridyl, piperidyl,



wherein W_1 is selected from hydrogen, fluoro and chloro; and



wherein W_2 is selected from hydrogen and



a is an integer from 1 to 5 and b is 0 or an integer from 1 to 5; with the proviso that the sum of a and b is not greater than 5.

* C L M S *

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