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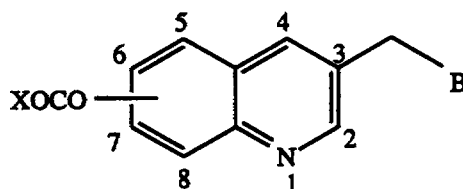
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SUBSTITUTED QUINOLINE HERBICIDE INTERMEDIATES
AND PROCESS

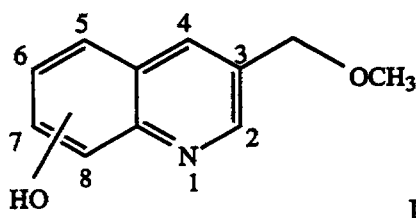
The invention relates to substituted quinoline intermediates useful in the synthesis of herbicides such as 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolidinyl)-5-methoxymethylnicotinic acid. It also
5 relates to a process for preparing the herbicide intermediates 3-methoxy- methyl-5,6,7- or 8-hydroxyquinoline.

The invention is herbicide intermediate
10 compounds of the formula



wherein X is straight or branched C₁-C₆ alkyl, phenyl,
15 -O-phenyl,
-O-C₁-C₄ straight or branched alkyl or $\text{N} \begin{matrix} \text{Y} \\ \text{Z} \end{matrix}$ wherein Y

and Z are independently H, straight or branched C₁-C₆ alkyl or phenyl, and B is H, halogen (eg chlorine or bromine) or a quaternary ammonium halide; and a process
20 for preparing compounds of the formula



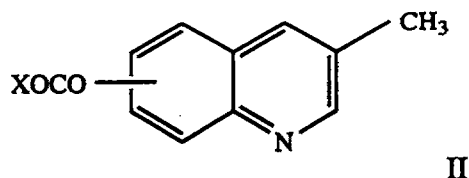
eg 7 or 8 hydroxy-, which comprises reacting a compound

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of the formula

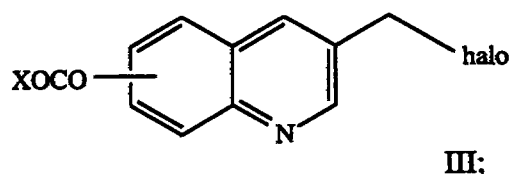


wherein X is a straight or branched C₁-C₆ alkyl, phenyl,
 5 -O-phenyl, -O-C₁-C₄ straight or branched alkyl

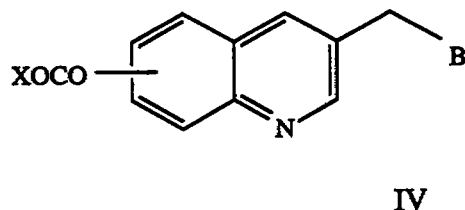
or N wherein Y and Z are independently H, straight

or branched C₁-C₆ alkyl or phenyl; reacting compound II
 with a radical halogenating reagent wherein the halogen
 is bromine or chlorine to form a compound of the formula

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reacting compound III with a tertiary amine without a
 reactive beta-hydrogen (eg an amine of formula R¹R²R³N
 where R¹⁻³ independently represent alkyl such as alkyl
 15 of 1-6 carbon atoms) to form a compound of the formula

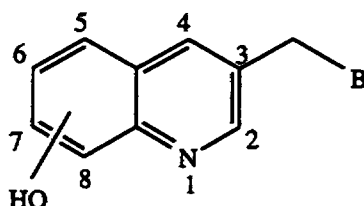


wherein B is a quaternary ammonium halide; and reacting
 compound IV with a base in methanol at a temperature
 20 within the range of about 120°C to about 180°C in a
 closed reactor to form a compound of formula I; or
 reacting compound IV with a base in methanol in the
 presence of a transition metal salt at a temperature



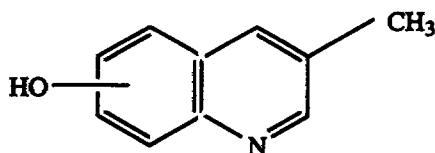
within the range of about 65°C to about 180°C in a closed reactor to form a compound of formula I.

The process to convert the compound IV to compound I may be carried out without isolating the compound of formula



wherein B is a quaternary ammonium halide, ie in a 'one-pot' reaction.

Compounds of formula II may be prepared by reacting a compound of formula



10

eg 7 or 8 hydroxy-, with an acylating agent of formula $(XCO)_2O$ or $XCOCl$ wherein X is as defined above, protected if necessary and removing the protecting group.

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Compounds of formula I such as 3-methoxymethyl-8-hydroxy quinoline are useful in the preparation of intermediates to herbicides such as the 5-methoxymethyl-2,3-pyridinedicarboxylic acid intermediate for the herbicide 2-(4-isopropyl-4-methyl-5-oxo-2-imidazolidinyl)-5-methoxymethylnicotinic acid of U.S. Patent 5,334,576.

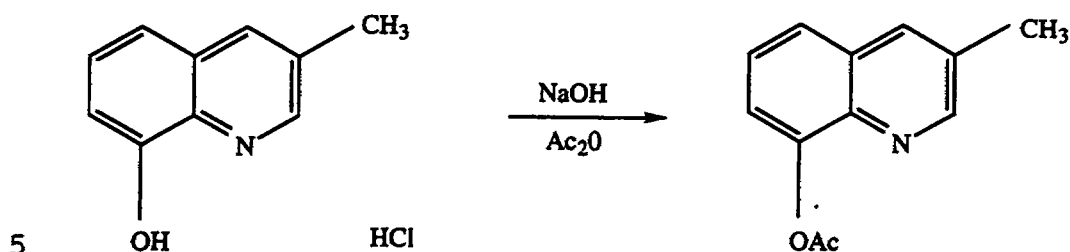
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The invention is further illustrated in the examples, below, but is not to be deemed limited thereby.

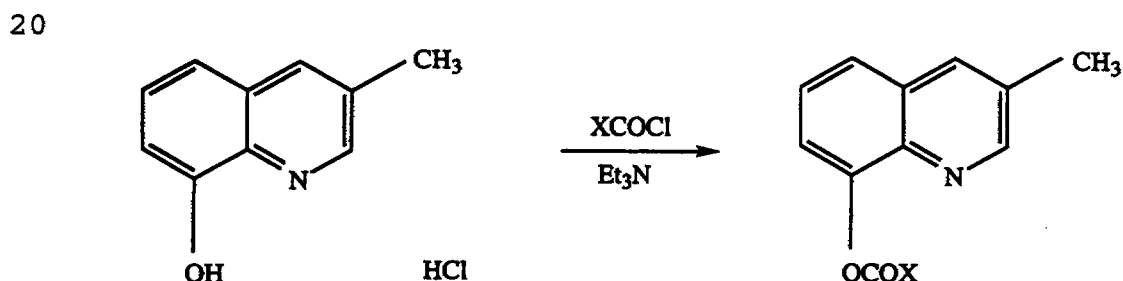
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Example 1: Preparation of Acylated 8-Hydroxy-3-Methylquinoline



A mixture of the hydrochloride salt of 8-hydroxy-3-methylquinoline (200 g, 1.02 mol) and sodium hydroxide (102 g, 2.55 mol) in 1000 ml water is treated with acetic anhydride (208 g, 2.04 mol) at 0-10°C over 1 hour and is allowed to stir at room temperature for 1 hour. An additional portion of acetic anhydride (50 g, 0.49 mol) is added and the resulting mixture is stirred for one more hour. Saturated sodium bicarbonate (100 ml) is added dropwise. The crude product is collected by filtration, washed with water, and dried at 60°C under vacuum. Recrystallization from ethyl acetate and heptane affords white needles of 8-acetoxy-3-methylquinoline (168.5 g, 82% yield).



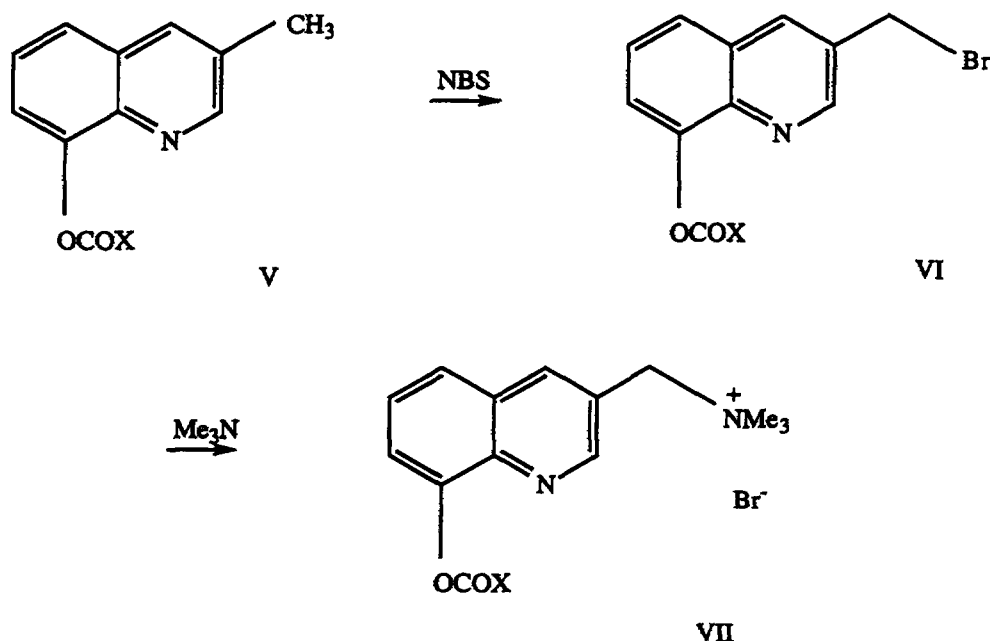
A mixture of the hydrochloride salt of 8-hydroxy-3-methylquinoline (10 g, 0.051 mol) and triethylamine (15.5 g, 0.15 mol) in 100 ml methylene



chloride is treated with benzoyl chloride (10.8 g, 0.077 mol) at 0-10°C over 1 hour and is allowed to stir at room temperature for 3 hours. Water is added and the organic phase is washed with water 3 times and dried with magnesium sulfate. Evaporation and recrystallization from heptane/toluene gives 8-benzoyloxy-3-methylquinoline as pale yellow crystals (8.8 g, 65% yield).

Other acylated 8-hydroxy-3-methylquinolines are prepared similarly.

Example 2: Preparation of the Quaternary Salt



15

Wherein X is as defined above eg methyl and the 8-position is shown for example only.

A solution of 8-acetoxy-3-methylquinoline (168.5 g, 0.84 mol), N-bromosuccinimide (NBS) (177.9 g, 1.00 mol), and 2, 2'-azobisisobutyronitrile (AIBN) (6.7 g, 0.04 mol) in 1675 ml chlorobenzene is purged with

20



nitrogen, heated at 80-90°C under nitrogen for 2 hours, cooled to room temperature and filtered. The filtrate containing 8-acetoxy-3-bromomethylquinoline is mixed with acetone (700 ml) and treated with trimethylamine
5 (75.4 g, 1.28 mol) at 0-5°C, allowed to stir at 5-10°C for 30 minutes and then at room temperature for 1 hour and filtered. The filter cake is washed with acetone and dried at 60°C under vacuum to give (8-acetoxyquinolin-3-yl)methyl trimethyl ammonium bromide)
10 a white solid (180 g, 63% overall yield). Highest yield achieved: 77%.

Other acylated 8-acetoxy-3-methylquinolines give the corresponding quaternary salts in similar yields. Examples of X in compounds V, VI and VII are
15 CH₃, t-butyl and methoxy.

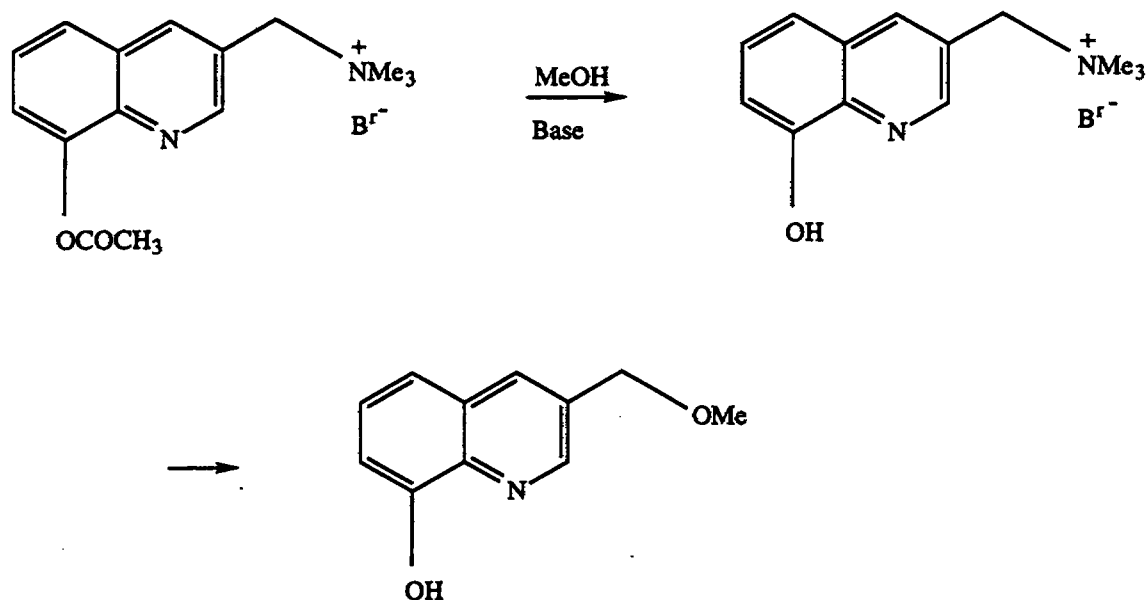
Variation in Conditions and Critical Factors for Preparation of the Quaternary Salt

- (1) Chlorobenzene is the recommended solvent.
- 20 (2) Concentration can be as low as 0.2 g acetate per 10 ml solvent or as high as 1 g acetate per 10 ml solvent. It can presumably be more concentrated as long as all reactants are soluble at reaction temperature.
- (3) Temperature is generally restricted to 80-95°C.
- 25 (4) Reaction is sluggish when temperature is below this range, and side reaction occurs when above this range.
- (5) The amount of AIBN can be from 2%-10%.
- (6) Reaction with trimethylamine is usually carried out -10-10°C.
- 30 (7) The parent compound, 8-hydroxy-3-methylquinoline, inhibits the bromination. Thus its content should be limited below 5%.
- (8) The bromination is carried out under nitrogen atmosphere. Oxygen can retard the reaction.

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Example 3: Preparation of 8-Hydroxy-3-Methoxymethyl
quinoline



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A solution of (8-acetoxyquinolin-3-yl)methyl trimethylammonium bromide (80 g, 0.24 mol) in 15% sodium methoxide in methanol (250 g, 0.69 mol) is heated at
 10 120°C in a pressure reactor for 18 hours and concentrated under reduced pressure. The residue is diluted with water and the pH is adjusted to 7-8 and filtered. The filter cake is washed with water and dried at 60°C under vacuum to give the title compound as
 15 a tan solid (40.63 g, 91% yield).

Examples 4-17 illustrate the methoxylation reaction of (8-acetoxyquinolin-3-yl)methyl trimethyl bromide using varied conditions. A methanol solution of the quaternary ammonium bromide and 3 equivalents of
 20 base, optionally with a catalyst, is heated at 65-180°C in a closed reactor for 16-96 hours and concentrated under reduced pressure. The residue is diluted with



water and the pH is adjusted to 7-8 and filtered. The filter cake is washed with water and dried at 60°C under vacuum to give a tan solid product.

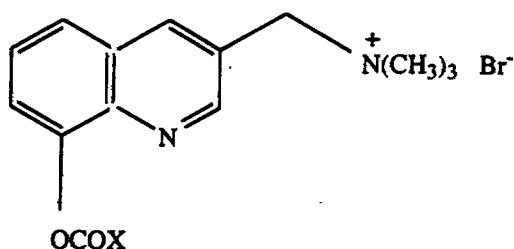
Example s	Conditions	Time (Hrs.)	Yields
4	no catalyst, NaOMe, 65°C	31	4%
5	no catalyst, LiOMe, 65°C	31	50%
6	5% CuSO ₄ , NaOMe, 65°C	31	65%
7	10% CuSO ₄ , NaOMe, 65°C	22	94%
8	10% CuSO ₄ , K ₂ CO ₃ , 65°C	96	73%
9	50% CuSO ₄ , K ₂ CO ₃ , 65°C	47	98%
10	5% FeSO ₄ , K ₂ CO ₃ , 65°C	96	67%
11	10% ZnCl ₂ , NaOMe, 65°C	20	38%
12	1-2% CuSO ₄ , K ₂ CO ₃ , 150°C	22	69-91%
13	1-2% CuSO ₄ , NaOMe, 120°C	17-21	~80%
14	no catalyst, 13% NaOMe, 120°C	19	73%
15	no catalyst, 15% NaOMe, 120°C	18	74%
16	no catalyst, NaOMe, 150°C	17	73%
17	no catalyst, NaOMe, 180°C	16	69%
18	no catalyst, K ₂ CO ₃ , 150°C	16.5	65%

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The above reaction was repeated using compounds of formula IV where B is trimethyl ammonium bromide ie

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wherein X is as defined above as the starting material.

When X of formula IV = Ph, a crude yield of
5 82% of the final product is obtained after heating the quaternary salt with potassium carbonate in methanol at 150°C for 18 hours.

When X of formula IV = OMe, a crude yield of
10 90% of the final product is obtained after heating the quaternary salt with potassium carbonate in refluxing methanol in the presence of 10% CuSO₄ for 22 hours.

Variation in Conditions and Critical Factors for The Methoxylation

- 15 (1) Transition metal salts such as but not limited to CuSO₄, FeSO₄, ZnSO₄, ZnCl₂ catalyze the reaction.
- (2) Temperature of the process may vary from 65°C to 180°C. Higher temperature may cause side-reaction. At lower temperature, the reaction may be very sluggish.
- 20 (3) Methanol is the preferred solvent. Diglyme or DMSO, along with NaOMe may also be used as a solvent.
- (4) Sodium methoxide and potassium carbonate are preferred for the reaction although other bases, such as LiOMe, KOMe, Ca(OMe)₂, Mg(OMe)₂, NaHCO₃, Na₂CO₃, KHCO₃,
- 25 CaCO₃, Me₃N, Et₃N, and pyridine can be used under appropriate conditions, such as higher temperature. In fact, the reaction may be carried out without added base since it produces base (Me₃N) during the reaction course.

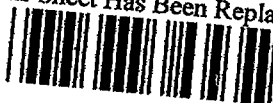
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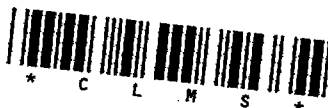


(5) Concentration is not critical. The highest concentration used was 15% NaOMe, or 3 g quaternary salt per 10 ml methanol, and the lowest was 0.2 g quaternary salt per 10 ml methanol.

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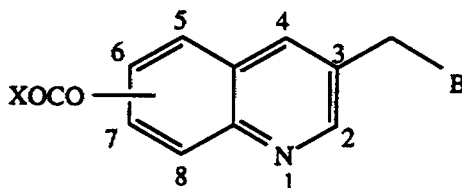


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CLAIMS

1. A compound of the formula



wherein X is straight or branched C_1 - C_6 alkyl, phenyl, $-O-C_1$ - C_4 straight or branched alkyl or $N \begin{matrix} \nearrow Y \\ \searrow Z \end{matrix}$ wherein Y

and Z are independently H, straight or branched C_1 - C_6 alkyl or phenyl and

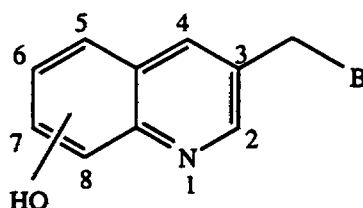
B is H, halogen, or a quaternary ammonium halide.

2. A compound according to Claim 1 wherein XOCO is in the 8 position.
3. A compound according to Claim 1 or Claim 2 wherein X is methyl, methoxy, phenyl or t-butyl.
4. A compound according to any one of Claims 1 to 3 wherein B is bromine or tertiary ammonium bromide.
5. A compound according to any one of Claims 1 to 3 wherein B is trimethyl ammonium bromide.
6. A compound as claimed in Claim 1 which is 8-acetoxy-3-methylquinoline, 8-acetoxy-3-bromomethylquinoline or (8-acetoxyquinolin-3-yl)methyltrimethylammonium bromide.

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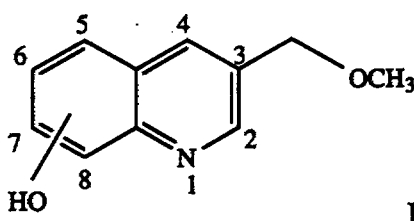
7. A compound of the formula



wherein B is a quaternary ammonium halide.

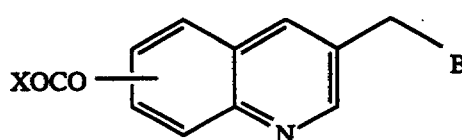
8. A compound according to claim 7 wherein the OH is in the 8 position and B is quaternary ammonium bromide.

9. A process for preparing a compound of the formula



which comprises

reacting a compound of the formula



IV

wherein B is a quaternary ammonium halide;
with a base in methanol at a temperature within the
range of about 120° to about 180°C in a closed reactor
to form a compound of formula I; or

reacting compound IV with a base in methanol
in the presence of a transition metal salt at a
temperature within the range of about 65°C to about
180°C in a closed reactor to form a compound of formula

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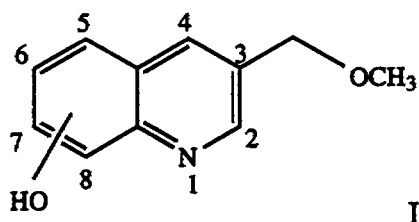
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I.

10. A process according to claim 9 wherein the compound IV is reacted with sodium methoxide in methanol in the presence of CuSO_4 at a temperature within the range of about 65°C to about 180°C .

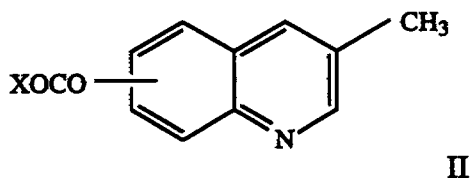
11. A process according to claim 10 wherein the reaction temperature is about 65°C in the presence of CuSO_4 to form compound I from compound IV.

12. A process for preparing a compound of the formula



which comprises

reacting a compound of the formula



wherein X is straight or branched $\text{C}_1\text{-C}_6$ alkyl, phenyl, -O-phenyl, -O- $\text{C}_1\text{-C}_4$ straight or branched alkyl or

$\text{N} \begin{cases} \text{Y} \\ \text{Z} \end{cases}$ wherein Y and Z are independently H, straight or

branched $\text{C}_1\text{-C}_6$ alkyl or phenyl with a radical halogenating reagent wherein the halogen is bromine or chlorine to form a compound of the formula

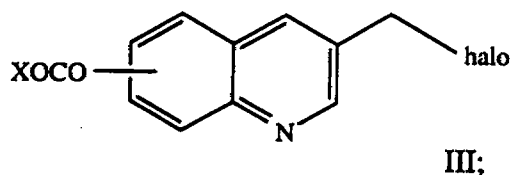
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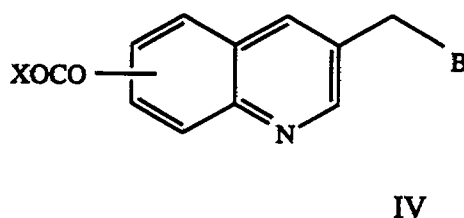


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reacting compound III with a tertiary amine without a reactive beta-hydrogen to form a compound of the formula



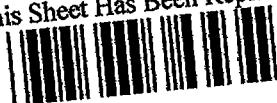
wherein B is a quaternary ammonium halide; and

reacting compound IV with a base in methanol at a temperature within the range of about 120° to about 180°C in a closed reactor to form a compound of formula I; or

reacting compound IV with a base in methanol in the presence of a transition metal salt at a temperature within the range of about 65°C to about 180°C in a closed reactor to form a compound of formula I.

13. A process according to Claim 12 wherein OH of compound I is in the 8 position, the radical halogenating agent to form compound III is N-bromosuccinimide, the tertiary amine to form compound IV is trimethyl amine and compound IV is reacted with sodium methoxide in methanol in the presence of CuSO₄ at a temperature within the range of about 65°C to about 180°C.

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14. A process according to Claim 13 wherein the reaction temperature is about 65°C in the presence of CuSO_4 to form compound I from compound IV.

15. A process according to Claim 12 wherein the acylating agent to form compound II is acetic anhydride, the radical halogenating agent to form compound III is N-bromosuccinimide, the tertiary amine to form compound IV is trimethyl amine and compound IV is reacted with sodium methoxide in methanol at a temperature of about 120°C.

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