

**United States Patent**  
**Diamond**

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[54] **N-(SUBSTITUTED)-POLYHYDROCY-  
CLOALKANO [B] QUINOLINES  
CARBOXAMIDES**

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260/287 R, 424/250, 424/257, 424/258  
[51] **Int. Cl.** .....C07d 39/00, C07d 51/70, C07d 37/02  
[58] **Field of Search** .....260/268 TR, 286

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[57] **ABSTRACT**

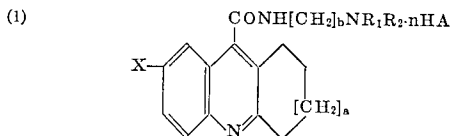
The compounds of this invention are useful in the treatment of mammals for auricular tachycardia. They are effective, potent anti-arrhythmic agents with a wide safety margin between effective doses and toxic doses. For example, one of the compounds of this invention is approximately equipotent to quinidine sulfate, with an equally long or longer duration of action, but is only one-half as toxic as quinidine sulfate.

**4 Claims, No Drawings**

# N-(SUBSTITUTED-POLYHYDROCYCLOALKANO[B] QUINOLINES CARBOXAMIDES

This invention relates to cycloalkano quinolines and the treatment of mammals with such cycloalkano quinolines as anti-arrhythmic drugs.

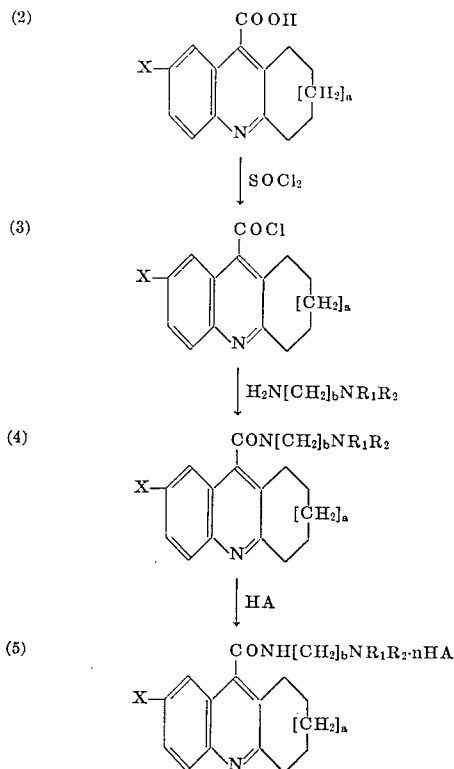
The cycloalkano quinolines of this invention have the following formula:



in which a is 0, 1 or 2; b is 2 or 3; X is hydrogen, halogen or lower alkoxy; HA is a non-toxic acid; n is 0, 1/2, 1 or 2; and R1 and R2 are hydrogen, lower alkyl or combined with the N to which they are connected to be a part of a saturated heterocyclic ring.

The methylene group  $[CH_2]_b$  may be straight or branched chain, such as methylene, ethylene or ethylidene. The halogen may be fluorine, chlorine, bromine or iodine. The lower alkoxy and lower alkyl each has preferably less than five carbon atoms, such as methyl, ethyl, propyl or isobutyl. The acid addition salts (HA) may be any non-toxic acid such as hydrochloric acid, sulfuric acid, citric acid or succinic acid. Examples of the saturated heterocyclic ring are piperidyl or pyrrolidyl.

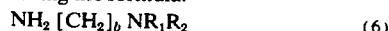
The compounds of this invention are produced in accordance with the following reaction scheme:



In the first step, a polyhydrocycloalkano[b] quinoline carboxylic acid, formula (2) above, is reacted with an excess of thionyl chloride in an inert solvent, such as chloroform by heating with agitation at reflux temperature for about 6 hours. The excess thionyl chloride and solvent are removed by vacuum distillation and the residue triturated with an inert solvent such as benzene and collected on a filter. The solid is triturated with hot solvent such as hot benzene to obtain a crude product. Recrystallization from a suitable inert solvent such as a mixture of chloroform and benzene results in the, corresponding acid chloride hydrochloride, formula (3) above.

In the subsequent steps of the process of producing the compounds of this invention, a suspension of an acid addition salt of a polyhydrocycloalkano[b] quinoline carbonyl chloride

is added dropwise to a solution in an inert solvent, such as toluene, of an amine having the formula:



During the addition, the reaction mixture is agitated at reflux temperature. After heating for a period of 4 to 12 hours, the mixture is cooled and washed several times with an aqueous solution of an alkali metal hydroxide such as sodium hydroxide and subsequently washed several times with water. The solid is filtered off. The inert solvent phase is dried over anhydrous potassium carbonate, filtered, and the inert solvent distilled off under vacuum. The resulting residue may be purified by any convenient means such as trituration with an inert solvent or dissolving in an inert solvent and decolorization with charcoal. The resulting product, formula (4) above, may be treated with an anhydrous non-toxic acid such as anhydrous hydrogen chloride gas to produce the acid addition salt, formula (5) above, and purified by any suitable means such as precipitation with ether followed by trituration with an inert solvent such as ethyl acetate.

A more comprehensive understanding of this invention is obtained by reference to the following examples.

## EXAMPLE I

### N-(2-DIETHYLAMINOETHYL)-6,7,8,9,10,11-HEXAHYDROCYCLOOCTA (B) QUINOLINE-12-CARBOXAMIDE DIHYDROCHLORIDE

Stage 1 — Preparation of 6,7,8,9,10,11-hexahydrocycloocta (b) quinoline-12-carbonyl chloride.

43 G (0.169 mole) of 6,7,8,9,10,11-hexahydrocycloocta (b) quinoline-12-carboxylic acid and 47.6 g (0.4 mole) of thionyl chloride in 75 cc of chloroform are heated with stirring at reflux temperature for 6 hours. The excess thionyl chloride and chloroform are removed by vacuum distillation, the amber-brown residue triturated with 300 cc of benzene, and collected on a filter. The solid is triturated with 250 cc of hot benzene and filtered to give a tan solid, 37 g, m.p. 209°–212° dec. Recrystallization from chloroform-benzene gives the nearly white acid chloride hydrochloride, 27 g, m.p. 211–12° dec.

Analysis: Calculated for  $C_{16}H_{17}Cl_2NO$ : C=61.95, H=5.52, N=4.52, Cl=22.86

Found: C=62.19, H=5.41, N=4.36, Cl=22.76

Stage 2 — Preparation of N-(2-diethylaminoethyl)-6,7,8,9,10,11-hexahydrocycloocta (b) quinoline-12-carboxamide dihydrochloride.

A suspension of 10 g of 6,7,8,9,10,11-hexahydrocycloocta (b) quinoline-12-carbonyl chloride hydrochloride in 200 cc of toluene is added dropwise during 1 hour to a solution of 20 g of N,N-diethylethylenediamine in 25 cc of toluene while stirring at reflux temperature. After heating for 8 hours, the mixture is cooled, washed with  $3 \times 150$  cc of 10% sodium hydroxide, followed by  $3 \times 200$  cc water, and 5.0 g of solid (A) filtered off. The toluene phase is dried over anhydrous  $K_2CO_3$ , filtered, and the toluene distilled off under vacuum to leave a gummy residue which solidifies after trituration with ethyl acetate, yield 4.5 g. The latter is taken up in 50 cc isopropanol, decolorized with charcoal and filtered. After treating with anhydrous hydrogen chloride gas, the solution is added slowly to 700 cc of ether to precipitate the dihydrochloride which is triturated with ethyl acetate, yield 4.5 g (B). The two solids (A and B) are combined in 25 cc of methanol, and the methanol is displaced with acetone to precipitate the dihydrochloride, 9.0 g, m.p. 242°–5° dec. Recrystallization from methanol-acetone gives 8 g white dihydrochloride 243°–5°.

Analysis: Calculated for  $C_{22}H_{33}Cl_2N_3O$ : C=61.97, H=7.80, N=9.85

Found: C=61.91, H=7.82, N=9.74

## EXAMPLE II

### N-(3-DIISOPROPYLAMINOPROPYL)-6,7,8,9,10,11-HEXAHYDROCYCLOOCTA (B)-QUINOLINE-12-CARBOXAMIDE DIHYDROCHLORIDE

The procedure in Example I is followed except that N,N-diisopropyl-1,3-propylenediamine is substituted for N,N-diethylethylenediamine.

## EXAMPLE III

## N-PIPERIDINOETHYL-6,7,8,9,10,11-HEXAHYDRO-CYCLOOCTA (B) QUINOLINE-12-CARBOXAMIDE DIHYDROCHLORIDE

The procedure in Example I is followed except that 2-piperidinoethylamine is substituted for N,N-diethylethylenediamine.

## EXAMPLE IV

## N-(PIPERAZINOETHYL)-6,7,8,9,10,11-HEXAHYDRO-CYCLOOCTA (B) QUINOLINE-12-CARBOXAMIDE DIHYDROCHLORIDE

The procedure in Example I is followed except that 2-piperazinoethylamine is substituted for N,N-diethylethylenediamine.

## EXAMPLE V

## N-(2-DIETHYLAMINOETHYL)-7,8,9,10-TETRAHYDRO-6H-CYCLOHEPTA [B] QUINOLINE-11-CARBOXAMIDE DIHYDROCHLORIDE

The procedure in Example I is followed except that the starting material is 7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline-11-carboxylic acid.

## EXAMPLE VI

## N-(2-DIETHYLAMINOETHYL)-6,7,8,9-TETRAHYDRO-CYCLOHEXA(B) QUINOLINE-10-CARBOXAMIDE DIHYDROCHLORIDE

The procedure in Example I is followed except that the starting material is 6,7,8,9-cyclohexa[b]quinoline-10-carboxylic acid.

## EXAMPLE VII

## 2-CHLORO-N-(2-DIETHYLAMINOETHYL)-6,7,8,9,10,11-HEXAHYDROCYCLOOCTA[B]QUINOLINE-12-CARBOXAMIDE DIHYDROCHLORIDE

The procedure in Example I is followed except that the starting material is 2-chloro-6,7,8,9,10,11-hexahydrocycloocta[b]quinoline-12-carboxylic acid.

## EXAMPLE VIII

## 2-METHOXY-N-(2-DIETHYLAMINOETHYL)-6,7,8,9,10,11-HEXAHYDROCYCLOOCTA[B]QUINOLINE-12-CARBOXAMIDE DIHYDROCHLORIDE

The procedure in Example I is followed except that the starting material is 2-methoxy-6,7,8,9,10,11-hexahydrocycloocta[b]quinoline-12-carboxylic acid.

The carboxamides and acid addition salts of this invention are effective in treating tachycardia and arrhythmias when administered to mammals. Their efficacy is illustrated by the reversal of aconitine-induced tachycardia and the reversal of ouabain-induced arrhythmias in mammals effected by the administration of N-(2-diethylaminoethyl)-6,7,8,9,10,11-hexahydrocycloocta (b) quinoline-12-carboxamide dihydrochloride.

Aconitine-induced tachycardia is produced by the initial administration of aconitine to a mammal. Aconitine is an alkaloid which is a peripheral and central stimulant. When applied directly to cardiac tissue in the area of the SA node, it increases the excitability and results in an auricular tachycardia of long duration. Antiarrhythmic drugs such as quinidine sulfate and procainamide can block the auricular tachycardia induced by aconitine due to an increase in refractory period.

As a test system, the anesthetized dog is maintained under positive pressure breathing, and the heart is exposed with open chest surgery. A small cotton pellet saturated with 0.05% aconitine is inserted in the right atrium in the area of the SA node with an immediate response of auricular tachycardis. The test compound is then given and the percent decrease in actual tachycardia is recorded as the positive end point.

Arrhythmias is effected by the administration of ouabain to a mammal. Ouabain is a cardiac glycoside which at larger

dosages is capable of producing arrhythmias similar to many forms of pathological arrhythmias. Ouabain increases vagus tone giving rise to a decreased atrial rate. At the same time it reduces the ventricular refractory period which permits the generation of ectopic beats and ultimately a ventricular tachycardia. The situation is generally characterized by a reversal in direction of the QRS complex. Anesthetized dogs are given ouabain at 70 mcg/kg, i.v. ECG (Standard Lead II) is monitored and if no ventricular tachycardia occurs in 30 minutes, a booster injection of 20 mcg/kg is given. The test compound is then given and the ECG pattern and heart rate are recorded. Antiarrhythmic drugs produce a reversion of the ECG pattern and a decrease in heart rate.

N-(2-diethylaminoethyl)-6,7,8,9,10,11-hexahydrocycloocta [b]quinoline-12-carboxamide dihydrochloride manifested activity in reversing aconitine induced tachycardia when given intravenously. The average effective dose of the tested compound in 3 dogs was 7.0 mg/kg which places that compound in the same potency range as quinidine sulfate (average effective dose is 6.6 mg/kg, i.v.). When given intraduodenally the tested compound was active at doses between 20 and 40 mg/kg in reversing aconitine-induced tachycardia. The onset time was delayed somewhat, but the length of activity was prolonged (greater than 4 hours). Quinidine sulfate under the same conditions was effective at doses between 30 and 40 mg/kg, duration of action greater than 3 hours. The tested compound reversed ouabain-induced arrhythmia in dogs at a dose of 5 mg/kg. (i.v.). The length of activity was greater than 2 hours.

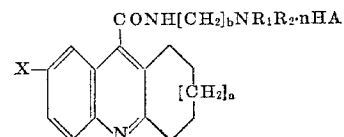
The carboxamides and their acid addition salts are nontoxic in dosages employed in the treatment of tachycardia in mammals, as shown by toxicity tests with N-(2-diethylaminoethyl)-6,7,8,9,10,11-hexahydrocycloocta(b)quinoline-12-carboxamide dihydrochloride.

In this testing male Swiss albino mice was randomly separated into groups of 10. The test compound was given orally as a water suspension containing 2 drops of Tween 80 per 10 ml. The animals were observed for mortality over a 5 day period. The LD<sub>50</sub> of the tested compound was calculated to be 1,280 mg/kg. (p.o.). The LD<sub>50</sub> of quinidine sulfate is 593 mg/kg. (p.o.).

The testing of N-(2-diethylaminoethyl)-6,7,8,9,10,11-hexahydrocycloocta(b)quinoline-12-carboxamide dihydrochloride in dogs indicates that it is an orally effective potent antiarrhythmic agent with a wide safety margin between effective doses and toxic doses. The compound is approximately equipotent to quinidine sulfate, with an equally long or longer duration of action, but is only one-half as toxic as quinidine sulfate. The data indicates that the therapeutic ratio of the tested compound is substantially more favorable than quinidine sulfate, which would meet one of the main objectives of research in the antiarrhythmic field.

What is claimed is:

1. A compound having the formula:



in which a is 0, 1 or 2; b is 2 or 3; X is hydrogen, halogen or lower alkoxy having less than five carbon atoms; HA is a non-toxic acid; n is 0, 1/2, 1 or 2, R<sub>1</sub> and R<sub>2</sub> are hydrogen, lower alkyl having less than five carbon atoms or combined with the N to which they are connected to be part of a saturated heterocyclic ring selected from the group consisting of piperidino, pyrrolidino and piperazino.

2. A compound of claim 1 in which n is 0.

3. A compound of claim 1 in which the lower alkoxy group has less than five carbon atoms.

4. A compound of claim 1 which is N-(2-diethylaminoethyl)-6,7,8,9,10,11-hexahydrocycloocta[b]quinoline-12-carboxamide dihydrochloride.

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