

1296754

## PATENT SPECIFICATION

(11)

1296754

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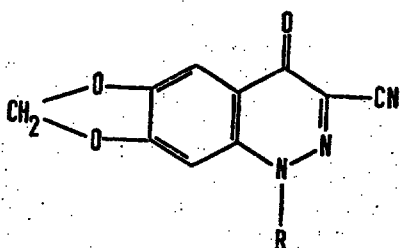
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(54) 1-SUBSTITUTED-6,7-METHYLENEDIOXY-4(1H)-  
 OXOCINNOLE-3-CARBONITRILES AND THEIR  
 PREPARATION

(71) We, ELI LILLY AND COM-  
 PANY, a Corporation organised and exist-  
 ing under the Laws of the State of Indiana,  
 United States of America, of 307 East  
 5 McCarty Street, Indianapolis, State of  
 Indiana, 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 parti-  
 10 cularly described in and by the following  
 statement:—

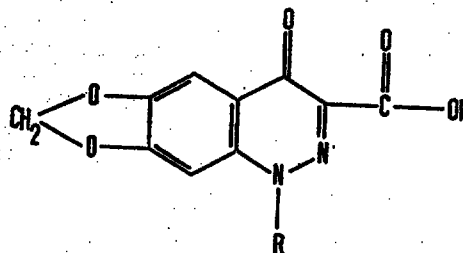
This invention relates to novel compounds  
 which are 1 - lower alkyl or alkenyl sub-  
 15 stituted - 6,7 - methylenedioxy - 4 (1H) -  
 oxocinnoline - 3 - carbonitriles having the  
 structure:



wherein R is methyl, ethyl, *n*-propyl, iso-  
 20 propyl, *n*-butyl,  $\beta$ -hydroxyethyl or allyl and  
 processes for their preparation.

Such carbonitrile compounds are useful  
 as intermediates in the preparation of carboxy-  
 lic acid of the following formula:

[Price 25p]



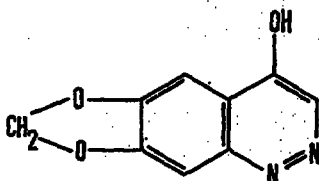
wherein R is methyl, ethyl, *n*-propyl, iso- 25  
 propyl, *n*-butyl, vinyl or allyl.

These carboxylic acids and the process of  
 preparing them are described and claimed in  
 our copending application No. 4817/70  
 (Serial No. 1296753) filed February 2, 1970. 30

The novel compounds of this invention can  
 be prepared by a multi-step synthesis starting  
 with the known compound, 2' - nitro - 4',5' -  
 methylenedioxy - acetophenone. The fore-  
 going starting material is reduced, utilizing  
 35 platinum dioxide as a catalyst, in a Parr  
 hydrogenation shaker at about 50 psi (pounds  
 per square inch) at a temperature of about  
 30—40°C. to form the new compound, 2' -  
 40 amino - 4',5' - methylenedioxy - aceto-  
 phenone. Those skilled in the art will recog-  
 nize that other catalysts, such as palladium  
 on carbon, or Raney Nickel, can also be  
 employed at pressures and temperatures other  
 45 than those specified; or that the reduction  
 can also be effected by using a suitable chemi-  
 cal reduction process.

The second step of the reaction sequence

comprises diazotizing and ring closing the amino compound to a cinnoline derivative by diazotizing the aminoacetophenone with an equimolar amount of a nitrous acid-generating nitrite in the presence of a five- to tenfold molar excess of a solution of hydrochloric acid at a temperature of 0°C, or below, then ring closing over a period of 3—24 hours at a temperature of 0—80°C, the preferred reaction conditions being 3—4 hours at 80°C. The reaction yields the known 6,7 - methylenedioxcinnoline - 4 - ol [Schofield and Simpson, *J. Chem. Soc.*, 519 (1945)] of the formula:



The cinnoline derivative can be brominated with bromine in the presence of an approximately equimolar amount of potassium acetate in a five- to tenfold molar excess of acetic acid at the refluxing temperature of the reaction mixture. The resulting new compound, 3 - bromo - 6,7 - methylenedioxcinnoline - 4 - ol, is converted to 6,7 - methylenedioxcinnoline - 4 - ol - 3 - carbonitrile by treating the bromo derivative with from about an equimolar amount to about a twofold molar excess of cuprous cyanide. The reaction is generally conducted in a five- to twenty-fold molar excess of dimethylformamide at atmospheric pressure for from 4—24 hours at a temperature of from about 50°C. to the refluxing temperature of the reaction mixture, preferably at refluxing temperatures for 4—6 hours.

Alkylation of 6,7 - methylenedioxcinnoline - 4 - ol - 3 - carbonitrile with a methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or allyl bromide, chloride, iodide or sulfate can be effected in accordance with known procedures in a polar organic solvent such as a C<sub>1</sub> to C<sub>8</sub> alkanol, a C<sub>2</sub> to C<sub>4</sub> alkanediol, diethyleneglycol, triethyleneglycol, dimethylformamide, dimethylacetamide and *N* - methylpyrrolidone, in the presence of a basic reagent to produce the corresponding 1 - methyl, ethyl, *n* - propyl, isopropyl, *n*-butyl, or alkyl - 6,7 - methylene - dioxy - 4(1H) - oxocinnoline - 3 - carbonitrile compounds of this invention.

As described and claimed in applicants copending application, the final step in the synthesis comprises hydrolysis of the carbonitrile to the corresponding carboxylic acid. The hydrolysis can be conveniently carried out with either an acid or a base. The preferred process comprises hydrolysis with concentrated hydrochloric acid in a reaction medium of acetic acid wherein the hydrochloric acid and the acetic acid are present

in a molar ratio of from 1:4 to 4:1 and the concentration of the acetic acid relative to the nitrile is in a molar ratio of from 5:1 to 20:1.

1 - Vinyl - 6,7 - methylenedioxy - 4(1H) - oxocinnoline - 3 - carboxylic acid is prepared by alkylating 6,7 - methylenedioxcinnoline - 4 - ol - 3 - carbonitrile with 1 - bromo - 2 - hydroxyethane to form 1 - ( $\beta$  - hydroxyethyl) - 6,7 - methylenedioxy - 4(1H) - oxocinnoline - 3 - carbonitrile and hydrolyzing the alkylated carbonitrile to the corresponding carboxylic acid as described above. The 1 - ( $\beta$  - hydroxyethyl) - 6,7 - methylenedioxy - 4(1H) - oxocinnoline - 3 - carboxylic acid is then esterified using *p* - toluene - sulfonyl chloride in pyridine to form the tosylate. Elimination of the tosylate using a strong base, such as sodium ethoxide in anhydrous ethanol, yields the desired 1 - vinyl - 6,7 - methylenedioxy - 4(1H) - oxocinnoline - 3 - carboxylic acid. Other suitable methods for effecting the elimination of the elements of water from the  $\beta$  - hydroxyethyl substituent can also be employed. A variety of such methods are known in the art.

This invention is further illustrated by the following examples:

#### Example 1

##### Preparation of 2' - Amino - 4',5' - methylenedioxyacetophenone

90 gm. (0.43 mole) of 2' - nitro - 4',5' - methylenedioxyacetophenone were suspended in 300 ml. of absolute ethanol and 200 mg. of platinum dioxide were added. The mixture was placed in a Parr hydrogenation shaker and reduced with hydrogen at 50 psi at a temperature of 30—40°C. for 3—4 hours until no further hydrogen uptake was observed. The solvent was evaporated from the reaction mixture under vacuum and the residue was taken up in 500 ml. of hot chloroform. The mixture was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from an 80:20 mixture of ethanol and water to yield about 70 gm. of yellowish-brown crystals of 2' - amino - 4',5' - methylenedioxyacetophenone having a melting point of 167—168°C. The yield was 90.7 per cent.

Analysis. C<sub>12</sub>H<sub>9</sub>NO<sub>2</sub>: Mol. Wt.: 179; Calc.: C, 60.33; H, 5.06; N, 7.82; Found: C, 60.60; H, 5.33; N, 7.75.

#### Example 2

##### Preparation of 6,7 - Methylenedioxcinnoline - 4 - ol

70 gm. (0.41 mole) of 2' - amino - 4',5' - methylene - dioxyacetophenone were added to 800 ml. of concentrated hydrochloric acid at room temperature. The resultant mixture was cooled to 0°C. and a solution of 35 gm. (0.5 mole) of sodium nitrite in 100 ml. of water was added dropwise while the tempera-

ture was maintained at 0°C, with stirring. Stirring was continued for 30 minutes after the sodium nitrite addition was completed. The resultant reaction mixture was filtered and the filtrate was warmed to 80°C. for 4 hours, allowed to cool to room temperature overnight to effect crystallization of the product, and filtered. The crystals so obtained were washed with water and then recrystallized from 600 ml. of an 80:20 mixture of dimethyl sulfoxide and water. 65 gm. of 6,7 - methylenedioxcinnoline - 4 - ol as light tan crystals were obtained. The product melted at 338°C. with decomposition. The yield was 83.6 percent.

Analysis:  $C_9H_8N_2O_3$ ; Mol. Wt.: 190; Calc.: C, 56.84; H, 3.18; N, 14.73; Found: C, 56.81; H, 2.93; N, 14.50.

#### Example 3

20 Preparation of 3 - Bromo - 6,7 - methylenedioxcinnoline - 4 - ol

60 gm. (0.3 mole) of 6,7 - methylenedioxcinnoline - 4 - ol were added to a solution comprising 30 gm. (0.3 mole) of anhydrous potassium acetate in 400 ml. of acetic acid. The resultant mixture was heated to reflux and a solution comprising 48 gm. (0.3 mole) of bromine in 100 ml. of acetic acid was added dropwise over a 2-hour period with stirring. After the addition of bromine was completed, the resultant mixture was stirred for an additional 30 minutes under reflux. The reaction mixture was allowed to cool to room temperature and then poured into 1 liter of ice water. The resultant precipitate was recovered by filtration and washed with 300 ml. of a 5-percent sodium bicarbonate solution. Recrystallization from an 80:20 mixture of dimethyl sulfoxide and water afforded 76 gm. of tan crystals of 3 - bromo - 6,7 - methylenedioxcinnoline - 4 - ol melting at 330°C. with decomposition. The yield was 94.3 percent.

Analysis:  $C_9H_7BrN_2O_3$ ; Mol. Wt.: 269; Calc.: C, 40.17; H, 1.87; N, 10.41; Br, 29.70; Found: C, 40.31; H, 1.85; N, 10.60; Br, 29.90.

#### Example 4

50 Preparation of 6,7 - Methylenedioxcinnoline - 4 - ol - 3 - carbonitrile

100 gm. (0.37 mole) of 3 - bromo - 6,7 - methylenedioxcinnoline - 4 - ol were added to a slurry comprising 63 gm. (0.70 mole) of cuprous cyanide in 1100 ml. of dry dimethylformamide. The resulting mixture was heated to reflux for 4-5 hours with stirring. Upon heating, the solution became homogeneous. On completion of the reaction, a heavy green precipitate formed. The resultant reaction mixture was cooled to room temperature and poured into a solution comprising 160 gm. of ferric chloride, 120 ml. of concentrated hydrochloric acid, and 250 ml.

of water. The resultant mixture was heated to 60°C. for 15-20 minutes, poured over 2 litres of cracked ice, and filtered. The yellow product was recrystallized from an 80:20 mixture of dimethyl sulfoxide and water yielding 75 gm. (93.8 percent) of 6,7 - methylenedioxcinnoline - 4 - ol - 3 - carbonitrile as tan crystals which melted at 330-340°C. with decomposition.

Analysis:  $C_{10}H_8N_2O_3$ ; Mol. Wt.: 215; Calc.: C, 55.82; H, 2.34; N, 19.53; Found: C, 55.74; H, 3.04; N, 18.63.

#### Example 5

Preparation of 1 - Ethyl - 6,7 - methylenedioxy - 4(1H) - oxocinnoline - 3 - carbonitrile

70 gm. (0.36 mole) of 6,7 - methylenedioxcinnoline - 4 - ol - 3 - carbonitrile were suspended in 500 ml. of dry dimethylformamide. 18 gm. (0.36 mole) of dry sodium hydride (prepared by washing 50 percent sodium hydride in mineral oil with Skelly B solvent) were added to the above-mentioned slurry with stirring. The mixture became homogenous as hydrogen was evolved. After the cessation of hydrogen evolution, 63 gm. (0.40 mole) of ethyl iodide were added dropwise at room temperature with stirring. Stirring was continued for 1 hour after the addition of the ethyl iodide was completed. The resultant reaction mixture was then heated to 100°C. for 2 hours, cooled to room temperature, and poured into 1 liter of ice water and made acidic with hydrochloric acid. The precipitate which was formed was removed by filtration and recrystallized from an 80:20 mixture of dimethyl sulfoxide and water. Fifty grams, a yield of 62.5 percent, of 1 - ethyl - 6,7 - methylenedioxy - 4(1H) - oxocinnoline - 3 - carbonitrile as light tan crystals which melted at 268-269°C. were recovered.

Analysis:  $C_{12}H_{10}N_2O_3$ ; Mol. Wt.: 243.22; Calc.: C, 59.26; H, 3.73; N, 17.28; Found: C, 59.05; H, 3.74; N, 17.10. Ethyl sulfate may replace ethyl iodide in the above reaction.

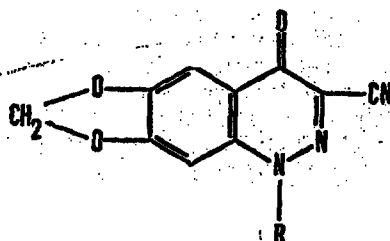
By following the foregoing procedure and substituting for the ethyl iodide employed therein, a methyl, *n*-propyl, isopropyl, *n*-butyl, or allyl bromide, chloride, iodide or sulfate, the following compounds are obtained:

- 1 - methyl - 6,7 - methylenedioxy - 4(1H) - oxocinnoline - 3 - carbonitrile
- 1 - *n* - propyl - 6,7 - methylenedioxy - 4(1H) - oxocinnoline - 3 - carbonitrile
- 1 - isopropyl - 6,7 - methylenedioxy - 4(1H) - oxocinnoline - 3 - carbonitrile
- 1 - *n* - butyl - 6,7 - methylenedioxy - 4(1H) - oxocinnoline - 3 - carbonitrile
- 1 - allyl - 6,7 - methylenedioxy - 4(1H) - oxocinnoline - 3 - carbonitrile



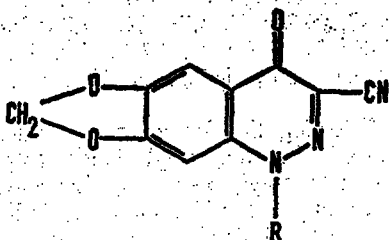
# WHAT WE CLAIM IS:—

1. A method for the preparation of a compound of the following formula:



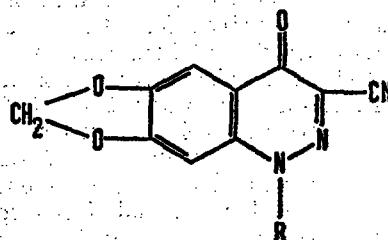
5 wherein R is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl,  $\beta$ -hydroxyethyl or allyl which comprises:

- (a) reducing 2'-nitro-4',5'-methylenedioxyacetophenone to 2'-amino-4',5'-methylenedioxyacetophenone;
- (b) diazotizing 2'-amino-4',5'-methylenedioxyacetophenone with nitrous acid and cyclizing to yield 6,7-methylenedioxycinnoline-4-ol;
- (c) treating 6,7-methylenedioxycinnoline-4-ol with bromine to produce 3-bromo-6,7-methylenedioxycinnoline-4-ol;
- (d) treating 3-bromo-6,7-methylenedioxycinnoline-4-ol with cuprous cyanide to form 6,7-methylenedioxycinnoline-4-ol-3-carbonitrile; and
- (e) alkylating 6,7-methylenedioxycinnoline-4-ol-3-carbonitrile with an alkyl, alkenyl or  $\beta$ -hydroxyethyl bromide, chloride, iodide or sulfate to form a 1-lower alkyl or alkenyl or  $\beta$ -hydroxyethyl substituted 6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile of the following formula:



wherein R is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl,  $\beta$ -hydroxyethyl, or allyl.

2. A compound of the following formula:



wherein R is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl,  $\beta$ -hydroxyethyl or allyl.

3. A compound according to claim 2, wherein the compound is 1-methyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile.

4. A compound according to claim 2, wherein the compound is 1-ethyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile.

5. A compound according to claim 2, wherein the compound is 1-(*n*-propyl)-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile.

6. A compound according to claim 2, wherein the compound is 1-isopropyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile.

7. A compound according to claim 2, wherein the compound is 1-(*n*-butyl)-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile.

8. A compound according to claim 2, wherein the compound is 1- $\beta$ -hydroxyethyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile.

9. A compound according to claim 2, wherein the compound is 1-allyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile.

10. The compounds according to claim 2 substantially as hereinbefore described with special reference to the Examples.

11. The method for the preparation of the compounds according to claim 2 hereinbefore described with special reference to the Examples.

12. 6,7-methylenedioxycinnoline-4-ol-3-carbonitrile.

13. A method according to claim 1, wherein the 2'-nitro-4',5'-methylenedioxyacetophenone is catalytically reduced in step (a).

14. A method according to claim 13 wherein wherein in step (e) the carbonitrile is alkylated with ethyl iodide or ethyl sulfate in the presence of a basic reagent to form 1-ethyl-6,7-methylenedioxy-4(1H)-oxocinnoline-3-carbonitrile.



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15. A compound according to claim 2 that has been prepared by a method according to either of claims 1 and 13.

- 5 16. A compound according to claim 2 wherein R is ethyl that has been prepared by a process according to either of claims 11 and 14.

BOULT, WADE & TENNANT,  
Chartered Patent Agents,  
34, Cursitor Street,  
London, EC4A 1PQ.

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