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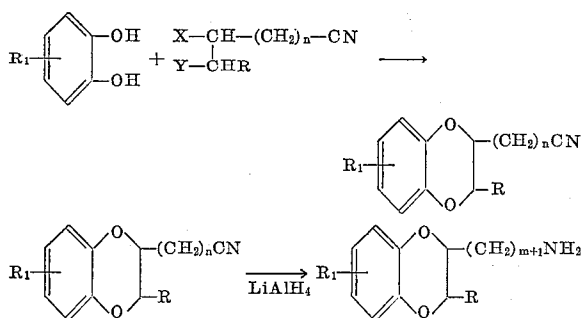
3,149,108

PREPARATION OF DERIVATIVES OF 1,4-BENZODIOXAN

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3 Claims. (Cl. 260—247.5)

This invention relates to a new process for making derivatives of 1,4-benzodioxan and, more specifically, to a process for preparing derivatives of 1,4-benzodioxan compounds which are substituted in their two-position by amino(lower) alkyl moieties.

The subject process for the synthesis of these 1,4-benzodioxan derivatives may be graphically and briefly illustrated by the following equations:



In these equations

R denotes hydrogen, lower alkyl; aralkyl—particularly, benzyl and aryl—particularly phenyl; but it may also represent heterocyclic radicals, such as, pyridyl, piperidyl, morpholinyl, etc.;

R₁ stands for hydrogen, halogen—particularly, chlorine and bromine; hydroxy; lower alkyl and lower alkoxy; X represents halogen, preferably, chlorine or bromine and n ranges from 0 to 4.

The term "lower alkyl" as used herein per se and as included in the term "lower alkoxy" means saturated monovalent aliphatic radicals of the general formula —C_nH_{2n+1} wherein n designates an integer of less than six and is inclusive of both straight-chain and branched-chain radicals.

The 1,4-benzodioxan compounds, referred to above, and particularly, many of their derivatives have been found to possess outstanding pharmacological properties, such as sympatholytic properties [Fourneau et al., Arch. intern. pharmacodynamie, 46, 178 (1933); Bovet et al., Arch. intern. pharmacodynamie, 55, 15 (1937); Goldenberg et al., J. Am. Med. Assoc., 135, 971 (1947)], Central depressant properties (Mills, Abstracts, 132nd Meeting, Am. Chem. Soc., New York, Sept. 1957, 7-0; U.S. Patent 2,906,757 and U.S. Patent 2,922,744), and adrenergic blocking properties [Rossi et al., J. Am. Pharm. Assoc., 48, 472 (1957) and ibid. 48, 409 (1959)].

Many of these pharmaceutical agents have been prepared by using as starting material 2-amino(lower)alkyl-1,4-benzodioxan. 2-aminomethyl-1,4-benzodioxan, for instance, can be synthesized by the three-step procedure carried out by G. B. Marini-Betolo et al. in Gazz. Chim. Ital., 83, 144 (1953). Catechol was refluxed with epichlorohydrin to yield 1,4-benzodioxan-2-methanol. This was obtained in 90% yield crude and 60% yield pure. On treatment with thionyl chloride, 1,4-benzodioxan-2-methanol was allegedly converted in 90% yield to 2-chloromethyl-1,4-benzodioxan. However, when this conversion method was repeated, the yield proved to be no better than 46% of pure material. Upon treating 2-

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chloromethyl-1,4-benzodioxan under prolonged heating with alcoholic or gaseous ammonia as described in U.S. Patent 2,366,102, there is obtained 2-aminomethyl-1,4-benzodioxan. No yield is given for this conversion. But it has been found when following this procedure that this is obtained only in 15% yield from 2-chloromethyl-1,4-benzodioxan. This last step, in addition to affording only low yields of the desired product, must be carried out under high pressure and is by no means a simple conversion. The overall yield for this three-step process, as described in the literature, is 5.8%.

2-aminomethyl-1,4-benzodioxan has also been synthesized in somewhat better yield in three steps in accordance with a method described in Koo et al., J. Am. Chem. Soc., 77, 5373 (1955) and Koo, J. Organic Chemistry, 26, 339 (1961) as follows: Catechol was condensed with ethyl 2,3-dibromopropionate in the presence of potassium carbonate, giving ethyl 1,4-benzodioxan-2-carboxylate in a yield of 76%. Ammoniation of this afforded 1,4-benzodioxan-2-carboxamide in 94% yield. Reduction of the carboxamide with lithium aluminum hydride proceeded in 82% yield to the desired product. The overall yield for this process was 58%.

3-aminomethyl-2-methyl-1,4-benzodioxan was also synthesized in three steps by Koo et al., J. Org. Chem., 26, 339 (1961) by condensing catechol with ethyl 2,3-dibromobutyrate in the presence of potassium carbonate giving, in 30% yield, ethyl 3-methyl-1,4-benzodioxan-2-carboxylate. Ammoniation of this ester afforded 3-methyl-1,4-benzodioxan-2-carboxamide in 80% yield. Reduction of the carboxamide with lithium aluminum hydride gave 2-aminomethyl-3-methyl-1,4-benzodioxan in 70% yield. The overall yield for this process was 16.8%.

Derivatives of 2-amino(lower)alkyl-1,4-benzodioxan have heretofore also been prepared from different intermediates, but they could be synthesized more economically by employing 2-amino(lower)alkyl-1,4-benzodioxan as starting material.

It is, therefore, a primary object of this invention to prepare 2-amino(lower)alkyl-3-substituted or unsubstituted-1,4-benzodioxan by a shorter, simpler and more economical procedure.

It has now been found that 2-amino(lower)alkyl-3-substituted or unsubstituted-1,4-benzodioxan can be produced readily by a novel procedure which involves merely two steps giving surprisingly and unexpectedly overall yields as high or higher than those which have heretofore been obtained and reported for the older three-step processes. As illustrated above, this method involves reacting catechol or a substituted catechol with an appropriate dihaloalkanoic acid nitrile to produce the corresponding cyano derivative of 1,4-benzodioxan in yields as high as 90%. Reduction of the cyano derivative proceeds readily to 2-amino(lower)alkyl-3-substituted or unsubstituted-1,4-benzodioxan—in yields as high as 77%. The combined yield for the two-step procedure for, e.g., 2-aminomethyl-3-methyl-1,4-benzodioxan is 42%—compared with 16.8% by the best procedure described in the literature and for 2-aminomethyl-1,4-benzodioxan is essentially the same as that previously reported in the best literature process, i.e., 54%—compared with 58%. It is thus clear that the present process affords 2-amino(lower)alkyl-3-substituted or unsubstituted 1,4-benzodioxan by a simpler and more direct process than those reported in the literature in yields equal to or better than the yields previously reported in the literature.

More specifically, the process of this invention contemplates as first step refluxing for several hours of catechol or a substituted catechol, dissolved in, preferably, dry acetone as inert solvent, with a dibromo(lower)alkanoic acid nitrile in the presence of potassium carbonate as acid

binding agent to produce a 2-cyano-3-substituted or unsubstituted-1,4-benzodioxan or a 2-cyano(lower)alkyl-3-substituted or unsubstituted-1,4-benzodioxan as intermediate, and as second step refluxing for several hours this intermediate with lithium aluminum hydride, suspended in ether, to produce the desired 2-amino(lower)alkyl-3-substituted or unsubstituted-1,4-benzodioxan.

In addition to potassium carbonate, such other acid binding agents as potassium hydroxide, sodium carbonate and sodium hydroxide, calcium carbonate and their equivalents may be employed. In fact, it is possible to use any basic compound that is sufficiently alkaline to bind hydrohalogenic acid set free during the reaction.

As equivalents for acetone as inert solvent for the catechol, it is practicable to use such organic solvents as, benzene, toluene, dibutylether, etc., while as diluent for lithium aluminum hydride in addition to ether, also tetrahydrofuran, dioxan, and their equivalents may be employed.

It is further apparent to men skilled in the art that the range of practicable equivalents is wider than explicitly circumscribed hereinabove. Therefore, any and all such practicable equivalents are within the scope of this invention.

The starting materials, substituted or unsubstituted catechols and dibromo(lower)alkanoic acid nitriles are respectively, commercially available or available by synthesis, e.g., according to the following literature references: Moureau, Annales de Chimie et de Physique [7] 2, 189 (2,3-dibromopropionitrile); Lespieau, Comptes rendus de l'Academie des Sciences, 137, 262 (3,4-dibromobutyronitrile); Palmer, American Chemical Journal, 11, 91 (2,3-dibromobutyronitrile); etc.

This new procedure may further be exemplified more specifically by the following examples wherein the temperatures are given in degrees centigrade. It is to be understood, however, that the examples are illustrative of the compounds which may be prepared in accordance with the inventive concept and of the method for their synthesis and are not to be construed as limiting the invention to the particular compounds or methods specifically described.

EXAMPLE I

2-Aminomethyl-1,4-Benzodioxan

(A) 2-cyano-1,4-benzodioxan.—To a solution of 51.7 g. (0.47 mole) of catechol in 250 ml. of dry acetone was added 34.5 g. (0.25 mole) of anhydrous potassium carbonate and then dropwise with stirring and gentle refluxing, 25.0 g. of 2,3-dibromopropionitrile. Another 34.5 g. of potassium carbonate and 25.0 g. of the 2,3-dibromopropionitrile was added similarly, and this was repeated twice more, using altogether 138 g. of potassium carbonate and 100.0 g. of 2,3-dibromopropionitrile. Stirring and refluxing was continued for 20 hours. The solution was then cooled and the solid potassium bromide filtered off. The cake was washed with acetone and the filtrate concentrated to a dark oil which was extracted into ether and washed with water and sodium bicarbonate solution. The ethereal solution was dried over anhydrous magnesium sulfate and concentrated to 74.9 g. (99%) of an amber oil. The oil was distilled to give 53.1 g. (70%) of 2-cyano-1,4-benzodioxan; B.P. 116–119°/0.15 mm.; n_D^{25} 1.5443.

(B) 2-aminomethyl-1,4-benzodioxan.—To 14 g. of lithium aluminum hydride in 500 ml. ether was added dropwise 48.3 g. of 2-cyano-1,4-benzodioxan with stirring and refluxing for 12 hours. The mixture was decomposed first with cold water and then with 300 ml. of 20% sodium potassium tartrate solution. The ether solution was dried and evaporated. The residue was distilled at 92–94°/0.3 mm.; n_D^{25} 1.5554. The yield of the desired product as colorless oil was 38.1 g. (77%). J. Koo, J. Org. Chem. 26, 339 (1961) reported B.P. 82–83°/0.75 mm. and n_D^{25} 1.5554.

EXAMPLE II

2-Aminoethyl-1,4-Benzodioxan

(A) 2-cyanomethyl-1,4-benzodioxan.—To a solution of 110.0 g. (1.0 mole) of catechol in 800 ml. of dry acetone was added first 114.0 g. (0.826 mole) of anhydrous potassium carbonate and then, dropwise with stirring and gentle refluxing, 62.5 g. (0.275 mole) of 3,4-dibromobutyronitrile. Another 114.0 g. of potassium carbonate and 62.5 g. of the 3,4-dibromobutyronitrile was added similarly, and this was repeated twice more, using altogether 455.4 g. (3.30 moles) of potassium carbonate and 250.0 g. (1.10 moles) of nitrile. Stirring and refluxing was continued for 18 hours. The mixture was then cooled and solid potassium bromide filtered off. The cake was washed with acetone. The acetone solutions were concentrated to a dark oil which solidified on standing. Yield: 173 g. (99%); M.P. 55–58°. The crude material was further purified to a white solid which melted at 65–66° after recrystallization from isopropyl alcohol.

(B) 2-aminoethyl-1,4-benzodioxan.—To 14 g. of lithium aluminum hydride, suspended in 500 ml. of ether, was added 52.5 g. of 2-cyanomethyl-1,4-benzodioxan (M.P. 55–58°) in ether with stirring and refluxing for 12 hours. The mixture was first decomposed with cold water and then with 300 ml. of 20% sodium potassium tartrate solution. The ether was dried and evaporated. The residue was distilled at 105–110°/0.4 mm. to give 14.2 g. (26%) of the desired compound as colorless oil; n_D^{26} 1.5502.

The oil was dissolved in ether and HCl gas was introduced. The colorless salt which separated was recrystallized from ethanol-ether to give a pure product; M.P. 157–159°.

EXAMPLE III

2-Aminomethyl-3-Methyl-1,4-Benzodioxan

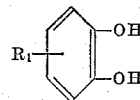
(A) 2-cyano-3-methyl-1,4-benzodioxan.—To a solution of 24.2 g. (0.22 moles) of catechol in 100 ml. of dry acetone was added 75.9 g. (0.55 mole) of anhydrous potassium carbonate, then dropwise with stirring and gentle refluxing 50.0 g. (0.22 mole) of 2,3-dibromobutyronitrile. Stirring and refluxing continued for 36 hours. The mixture was then cooled and the salt filtered off. The cake was washed with acetone and the acetone solution was concentrated to 34.2 g. (98% yield) of an oil which was distilled, yield: 22.0 g. (57%) of a colorless oil; B.P. 90–98°/0.25 mm., n_D^{25} 1.5280.

(B) 2-aminomethyl-3-methyl-1,4-benzodioxan.—To 10 g. of lithium in 400 ml. of ether was added 25.25 g. of 2-cyano-3-methyl-1,4-benzodioxan with stirring and gentle refluxing for 16 hours. The reaction mixture was decomposed first with cold water and then 20% potassium sodium tartrate solution. The ether layer was separated, washed with cold water, dried and filtered. Evaporation of the ether left an oily residue, which was distilled at 94–96°/0.1 mm. to give 11.8 g. (44%) of a colorless oil; n_D^{26} 1.5449.

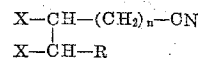
This application is a continuation-in-part of application Serial Number 85,455, filed January 30, 1961, now abandoned.

What is claimed is:

1. A process which comprises refluxing a catechol of the formula



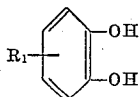
wherein R_1 is a member of the group consisting of hydrogen, chlorine, bromine, hydroxy, lower alkyl and lower alkoxy, with a dihalo(lower)alkanoic acid nitrile of the formula



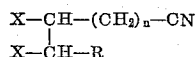
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wherein R is selected from the group consisting of hydrogen, lower alkyl, benzyl, phenyl, pyridyl, piperidyl and morpholinyl, X is taken from the group consisting of chlorine and bromine, and n has a value of 0 to 4, in the presence of an acid binding agent, refluxing the resulting cyano 1,4-benzodioxan obtained with lithium aluminum hydride and recovering the desired 2-amino(lower)alkyl-1,4-benzodioxan.

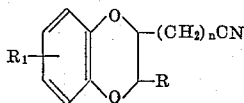
2. A process which comprises the steps of refluxing in an inert solvent a catechol of the formula



wherein R_1 is a member of the group consisting of hydrogen, chlorine, bromine, hydroxy, lower alkyl and lower alkoxy, with a dihalo(lower)alkanoic acid nitrile of the formula



wherein R is selected from the group consisting of hydrogen, lower alkyl, benzyl, phenyl, pyridyl, piperidyl and morpholinyl, X is taken from the group consisting of chlorine and bromine, and n has a value of 0 to 4, in the presence of an acid binding agent selected from the group consisting of a carbonate of alkali metals and alkaline earth metals for from 18 to 36 hours, refluxing the resulting cyano 1,4-benzodioxan obtained of the formula

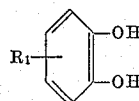


wherein R, R_1 and n are as defined hereinabove, with lithium aluminum hydride suspended in an inert diluent for from 12 to 16 hours and recovering the desired 2-amino(lower)alkyl-1,4-benzodioxan.

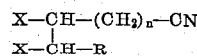
3. A process for preparing 2-amino(lower)alkyl-1,4-

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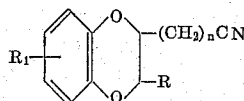
benzodioxan which comprises the steps of adding to a solution of a catechol of the formula



wherein R_1 is a member selected from the group consisting of hydrogen, chlorine, bromine, hydroxy, lower alkyl and lower alkoxy, in dry acetone, anhydrous potassium carbonate as acid binding agent and a dibromo(lower)alkanoic acid nitrile of the formula



wherein R is selected from the group consisting of hydrogen and lower alkyl, benzyl, phenyl, pyridyl, piperidyl and morpholinyl, X is taken from the group consisting of chlorine and bromine, and n has a value of 0 to 4, refluxing the reaction mixture thus obtained for from 18 to 36 hours, recovering and purifying the resulting cyano 1,4-benzodioxan of the formula



wherein R, R_1 and n are as defined hereinabove, adding said cyano 1,4-benzodioxan suspended in ether to an ether suspension of lithium aluminum hydride, refluxing the reaction mixture thus obtained for from 12 to 16 hours until the hydrogenation is substantially completed and recovering the desired 2-amino(lower)alkyl-1,4-benzodioxan.

References Cited in the file of this patent

- Koo et al.: J. Am. Chem. Soc., vol. 77, pages 5373-5375 (1955).
Koo: J. Org. Chemistry, vol. 26, page 339 (1961).

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

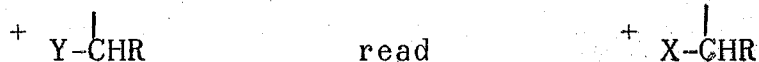
Patent No. 3,149,108

September 15, 1964

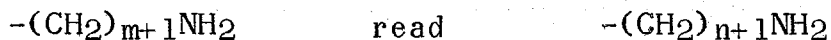
John Koo et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 1, lines 18 to 22, first equation, for that portion of the equation reading:



same column 1, lines 25 to 30, the last structure, upper right-hand portion reading:



Signed and sealed this 12th day of January 1965.

(SEAL)

Attest:

ERNEST W. SWIDER
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents