

PATENT SPECIFICATION

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(54) DI-ETHERIFIED 2,5-DIHYDROXY-3-AMINOMETHYL TETRAHYDROFURANS AND THEIR MANUFACTURE

(71) We, BASF AKTIENGESELLSCHAFT, a German Joint Stock Company of 6700 Ludwigshafen, Federal Republic of Germany, 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:—

The present invention relates to dietherified 2,5 - dihydroxy - 3 - amino - methyl - tetrahydrofurans and to their manufacture.

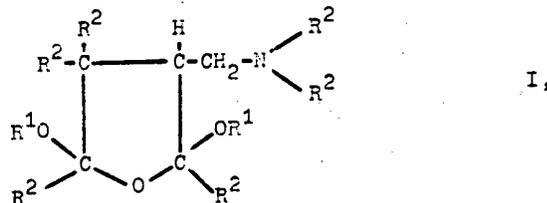
Houben-Weyl, Methoden der Organischen Chemie, Volume VI/3, pages 654—655, discloses that the tetrahydrofuran ring is split on hydrogenation with hydrogen in the presence of hydrogenation catalysts. Thus, 5 - methyl - 2 - ethyltetrahydrofuran is split over nickel - aluminum catalysts at 200°C to give heptanol and hexanol. The hydrogenation of alkylated tetrahydrofurans is stated to result in each case in splitting of the ring, and when using Raney nickel, paraffin hydrocarbons, which contain one carbon atom fewer, are stated to be obtained; for example, 2-propyltetrahydrofuran at 275°C gives hexane.

Houben-Weyl further discloses (loc. cit., pages 668, 669 and 674) that tetrahydrofuran and ammonia or primary amines in the presence of metal catalysts at elevated temperatures give pyrrolidines, whilst 2,5 - dichlorotetrahydrofuran and primary amines give pyrroles even at low temperatures.

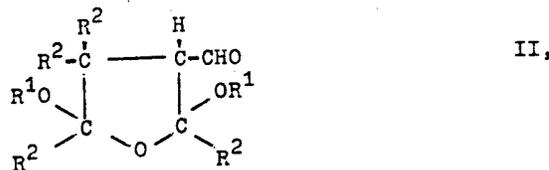
Acta Chem. Scand., 6 (1952), 667—670, and J. Org. Chem., 27 (1962), 2,466—2,470, disclose that certain dimethoxy-tetrahydrofurans and diethoxy-tetrahydrofurans react with specific primary amines to give pyrroles.

The manufacture of 3 - aminomethyltetrahydrofurans and especially of di - etherified 3 - aminomethyl - 2,5 - dihydroxytetrahydrofurans has not previously been disclosed.

We have found that a dietherified 2,5 - dihydroxy - 3 - aminomethyl - tetrahydrofuran of the formula



where the individual radicals R¹ and R² are identical or different and each is an aliphatic radical, and the individual radicals R² may also each be hydrogen, is obtained in an advantageous manner when a dietherified 2,5 - dihydroxy - 3 - formyl - tetrahydrofuran of the formula

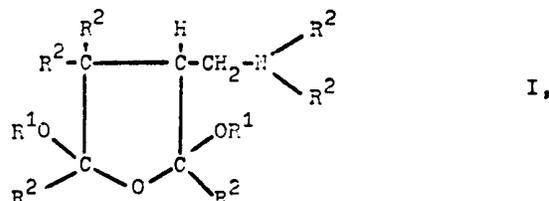


where R¹ and R² have the above meanings, is reacted with ammonia or an amine of the formula



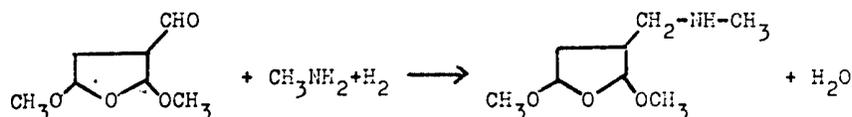
where R² has the above meaning, and hydrogen in the presence of a hydrogenation catalyst.

The resulting dietherified 2,5 - dihydroxy - 3 - aminomethyltetrahydrofurans of the formula



where the individual radicals R¹ and R² are identical or different and each is an aliphatic radical, and the individual radicals R² may also be hydrogen, are new compounds.

When 2,5 - dimethoxy - 3 - formyl - tetrahydrofuran and methylamine are used, the reaction can be represented by the equation:



Compared to the prior art, the process of the invention is able to give new dietherified 2,5 - dihydroxy - 3 - amino - methyltetrahydrofurans in a simple and economical manner, and in good yield and high purity. All these advantageous results are surprising, since, taking into the account the above publications, it would have been expected that the reaction would result in the formation of alkanols, paraffin hydrocarbons, pyrroles and/or pyrrolidines, i.e. heterogeneous mixtures of numerous components.

The dietherified 2,5 - dihydroxy - 3 - formyl - tetrahydrofurans used as the starting material II may be obtained by hydroformylation of corresponding dietherified 2,5 - dihydroxy - 2,5 - dihydrofurans in the presence of a rhodium catalyst, e.g. by the method described in Synthesis 1973, page 422.

To produce the product I the starting material II may be reacted with the starting material III in the stoichiometric amount or in an excess, preferably in an amount of from 1 to 12 moles of starting material III per mole of starting material II. Preferred starting materials II and III and, accordingly, preferred end products I are those where the individual radicals R¹ and R² are identical or different and each is alkyl of 1 to 8 carbon atoms, preferably of 1 to 4 carbon atoms, and the individual radicals R² may also each be hydrogen. The individual radicals R² in the starting compound II may be different from one another, the individual radicals R² in the starting material III can also be different from one another and/or the radicals R² of the starting material II can be different from the radicals R² of the starting material III. The alkyl or other aliphatic radicals R² and R¹ may furthermore be substituted by one or more groups which are inert under the reaction conditions, e.g. alkyl of 1 to 4 carbon atoms or carbalkoxy.

Examples of suitable starting materials II are 4 - methyl-, 4 - ethyl-, 4 - propyl-, 4 - isopropyl-, 4 - n - butyl-, 4 - iso - butyl-, 4 - tert. - butyl-, 4 - sec. - butyl-, 2 - methyl-, 2 - ethyl-, 2 - propyl-, 2 - isopropyl-, 2 - n - butyl-, 2 - iso - butyl-, 2 - tert. - butyl-, 2 - sec. - butyl-, 5 - methyl-, 5 - ethyl-, 5 - propyl-, 5 - isopropyl-, 5 - n - butyl-, 5 - iso - butyl-, 5 - tert. - butyl-, 5 - sec. - butyl-, 4,4 - dimethyl-, 4,4 - diethyl-, 4,4 - dipropyl-, 4,4 - diisopropyl-, 4,4 - dibutyl-, 4,4 - di - sec. - butyl-, 4,4 - di - isobutyl-, 4,4 - di - tert. - butyl-, 2,4 - dimethyl-, 2,4 - diethyl-, 2,4 - dipropyl-, 2,4 - diisopropyl-, 2,4 - dibutyl-, 2,4 - di - sec. - butyl-, 2,4 - diisobutyl-, 2,4 - di - tert. - butyl-, 2,5 - dimethyl-, 2,5 - diethyl-, 2,5 -

dipropyl-, 2,5 - diisopropyl-, 2,5 - dibutyl-, 2,5 - di - sec. - butyl-, 2,5 - diisobutyl-, 2,5 - di - tert. - butyl-, 4,5 - dimethyl-, 4,5 - diethyl-, 4,5 - dipropyl-, 4,5 - diisopropyl-, 4,5 - dibutyl-, 4,5 - di - sec. - butyl-, 4,5 - di - isobutyl- and 4,5 - di - tert. - butyl - 3 - formyl - 2,5 - dimethoxy - tetrahydrofuran, as well as 2,5 - diethoxy-, 2,5 - dipropoxy-, 2,5 - diisopropoxy-, 2,5 - dibutoxy, 2,5 - diisobutoxy-, 2,5 - di - sec. - butoxy- and 2,5 - di - tert. - butoxy - compounds corresponding to the above 2,5 - dimethoxy- compounds.

Suitable starting materials III are ammonia, methylamine, ethylamine, propylamine, isopropylamine, n - butylamine, sec. - butylamine, isobutylamine, tert. - butylamine, dimethylamine, diethylamine, di - n - propylamine, diisopropylamine, di - n - butylamine, diisobutylamine, di - sec. - butylamine and di - tert. - butylamine, and amines with different substituents from amongst those mentioned above, e.g. N - methyl - N - ethylamine.

The reaction is in general carried out at from 30 to 200°C, preferably from 60 to 100°C, especially from 70 to 90°C, under atmospheric pressure or, advantageously, under superatmospheric pressure, preferably at from 10 to 350 bars, especially from 50 to 250 bars, advantageously from 100 to 200 bars, continuously or batchwise. The use of solvents which are inert under the reaction conditions is advantageous. Examples of suitable solvents are aromatic hydrocarbons, e.g. toluene, ethylbenzene, o-, m- and p-xylene, isopropylbenzene and methyl-naphthalene, halohydrocarbons, especially chlorohydrocarbons, e.g. tetrachloroethylene, 1,1,2,2 - or 1,1,1,2 - tetrachloroethane, amyl chloride, cyclohexyl chloride, dichloropropane, methylene chloride, dichlorobutane, isopropyl bromide, n - propyl bromide, butyl bromide, chloroform, ethyl iodide, propyl iodide, chloronaphthalene, dichloronaphthalene, carbon tetrachloride, 1,1,1- or 1,1,2 - trichloroethane, trichloroethylene, pentachloroethane, 1,2 - dichloroethane, 1,1 - dichloroethane, n - propyl chloride, 1,2 - cis - dichloroethylene, n - butyl chloride, 2-, 3- and iso - butyl chloride, chlorobenzene, fluorobenzene, bromobenzene, iodobenzene, o-, p- and m - dichlorobenzene, o-, p- and m - dibromobenzene, o- m- and p - chlorotoluene, 1,2,4 - trichlorobenzene, 1,10 - dibromodecane and 1,4 - dibromobutane, ethers and thioethers, e.g. ethyl propyl ether, methyl tert. - butyl ether, n - butyl ethyl ether, di - n - butyl ether, diisobutyl ether, diisoamyl ether, diisopropyl ether, anisole, phenetole, cyclohexyl methyl ether, diethyl ether, ethylene glycol dimethyl ether, tetrahydrofuran, dioxane, thioanisole and β,β' - dichlorodiethyl ether, esters, e.g. methyl acetate, methyl propionate, butyl acetate, ethyl formate, methyl phthalate, methyl benzoate, ethyl acetate and phenyl acetate, alkanols and cycloalkanols, e.g. ethanol, methanol, n - butanol, isobutanol, tert. - butanol, glycol, glycerol, n - propanol, isopropanol, amylalcohol, cyclohexanol, 2 - methyl - 4 - pentanol, ethylene glycol monoethyl ether, 2 - ethyl - hexanol, methylglycol, n - hexanol, isohexyl alcohol, isoheptyl alcohol, n - heptanol, 2 - ethylbutanol, nonyl alcohol, dodecyl alcohol and methylcyclohexanol, but especially those of 1 to 4 carbon atoms, sulfoxides, e.g. dimethylsulfoxide and diethylsulfoxide, dimethylsulfone, diethylsulfone, methylethylsulfone and tetramethylenesulfone, aliphatic or cycloaliphatic hydrocarbons, e.g. heptane, α -pinene, pinane, nonane, gasoline fractions within a boiling range of from 70 to 190°C, cyclohexane, methylcyclohexane, decalin, petroleum ether, hexane, naphtha, 2,2,4 - trimethylpentane, 2,2,3 - trimethylpentane, 2,3,3 - trimethylpentane and octane, and mixtures of the above. The solvents are advantageously used in an amount of from 30 to 10,000 per cent by weight, preferably from 50 to 500 per cent by weight, based on the starting material II.

The starting materials III may be added in any desired state, for example as gaseous or liquid ammonia or as a solution in a solvent which is inert under the reaction conditions.

The reaction is carried out with hydrogen in the presence of a hydrogenation catalyst. The hydrogenation catalyst used in general comprises one or more metals of atomic number from 24 to 29, as a rule being a cobalt or nickel catalyst, e.g. a sintered catalyst of one of these metals, which may contain up to 30 per cent by weight of copper, manganese, iron and/or chromium; the use of Raney nickel and especially of Raney cobalt is preferred. As a rule, the hydrogenation catalyst is added in an amount of from 0.5 to 50, preferably from 1 to 10, per cent by weight, based on starting material II. Hydrogen is as a rule used in an excess, advantageously of from 1 to 1,000, preferably from 3 to 100 moles of H₂, based on starting material II. As a rule, hydrogen is fed into the reaction mixture at the start, and in the course, of the reaction in such amount that at the reaction temperature

an appropriate reaction pressure is always set up. Inert gases, e.g. nitrogen, may also be used, in addition to hydrogen, in order to set up an appropriate pressure.

The reaction may be carried out as follows: the catalyst, with or without solvent, is introduced into a reactor, the reaction space is flushed with nitrogen, and the starting material III is added. Hydrogen is then forced in until the above reaction pressure is reached. The starting material II, with or without solvents, is now added. Before or after adding the hydrogen, the reaction mixture is brought to the above temperature and is kept thereat, whilst introducing further hydrogen, until no more hydrogen is consumed by the reaction; this in general requires from 2 to 12 hours. The reaction mixture is now cooled and filtered if appropriate. The end product is isolated from the filtrate by conventional methods, e.g. by fractional distillation.

The new compounds I obtainable by the process of the invention are valuable intermediates for the manufacture of pharmaceuticals, dyes, textile assistants and crop protection agents. For example, a pyrrole which is substituted in the 3-position but unsubstituted in the 2- and 5-position may be obtained from an end product I by reaction with a primary amine, preferably in the presence of a catalytic amount of a sulfonic acid, e.g. p - toluene - sulfonic acid, advantageously at from 40 to 200°C. Such pyrroles and their manufacture by such a reaction are described and claimed in our copending British Patent Application No. 41602/77 (Serial No. 1586792). The pyrroloacetic acid derivatives described in German Laid-Open Application DOS 2,261,965, which possess analgesic, anti-inflammatory and antipyretic properties, may be obtained similarly.

In the Examples which follow, parts are by weight.

EXAMPLE 1

3-Aminomethyl-2,5-dimethoxy-tetrahydrofuran

30 parts of Raney cobalt in 250 parts of ethanol are introduced into an autoclave. After flushing with nitrogen, 400 parts of ammonia are injected. The mixture is heated to 80°C and the pressure is brought to 150 bars by injecting hydrogen. 400 parts of 2,5 - dimethoxy - 3 - formyl - tetrahydrofuran are injected in the course of 5 hours whilst stirring. 250 parts of ethanol are then pumped in to flush the fittings of the equipment. The mixture is then stirred for a further 6 hours at 80°C and 150 bars. Thereafter the autoclave is cooled and let down, and the contents are subjected to fractional distillation. 297 parts of 3 - aminomethyl - 2,5 - dimethoxy - tetrahydrofuran (boiling point 95—97°C/15 mbar) are obtained.

EXAMPLE 2

3-Methylaminomethyl-2,5-dimethoxy-tetrahydrofuran

Using the method described in Example 1, with 400 parts of monomethylamine instead of ammonia, 372 parts of 3 - (N - methyl) - aminomethyl - 2,5 - dimethoxy - tetrahydrofuran (boiling point 95—97°C/25 mbar) are obtained.

EXAMPLE 3

3-Dimethylaminomethyl-2,5-dimethoxy-tetrahydrofuran

Using the method described in Example 1, with 350 parts of dimethylamine and 400 parts of 2,5 - dimethoxy - 3 - formyl - tetrahydrofuran, 290 parts of 3 - (N,N - dimethyl) - aminomethyl - 2,5 - dimethoxy - tetrahydrofuran (boiling point 86—87°C/15 mbar) are obtained.

EXAMPLE 4

3-Diethylaminomethyl-2,5-dimethoxy-tetrahydrofuran

Using the method described in Example 1, with 250 parts of diethylamine and 300 parts of 2,5 - dimethoxy - 3 - formyl - tetrahydrofuran, 51 parts of 3 - (N,N - diethyl) - aminomethyl - 2,5 - dimethoxy - tetrahydrofuran (boiling point 110°C/15 mbar) are obtained.

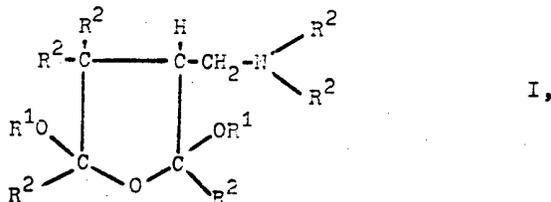
EXAMPLE 5

3-Isopropylaminomethyl-2,5-dimethoxy-tetrahydrofuran

On reacting 300 parts of 2,5 - dimethoxy - 3 - formyl - tetrahydrofuran with 250 parts of isopropylamine by the method described in Example 1, 110 parts of 3 - (N - isopropyl) - aminomethyl - 2,5 - dimethoxy - tetrahydrofuran (boiling point 155°C/15 mbar) are obtained.

WHAT WE CLAIM IS:—

1. A di - etherified 2,5 - dihydroxy - 3 - aminomethyl - tetrahydrofuran of the formula



5 where the individual radicals R¹ and R² are identical or different and each is an aliphatic radical, and the individual radicals R² may also each be hydrogen. 5

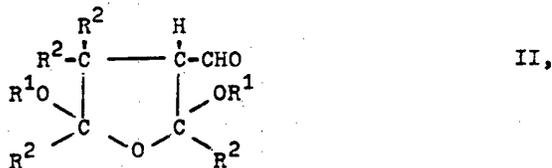
2. A di - etherified 2,5 - dihydroxy - 3 - aminomethyl - tetrahydrofuran as claimed in claim 1 in which R¹ denotes alkyl of 1 to 4 carbon atoms, the two radicals R¹ being identical.

10 3. A dietherified 2,5 - dihydroxy - 3 - aminomethyl - tetrahydrofuran as claimed in claim 1 or 2 in which R² denotes hydrogen or alkyl of 1 to 8 carbon atoms, the individual radicals R² being identical or different. 10

15 4. A dietherified 2,5 - dihydroxy - 3 - aminomethyl - tetrahydrofuran as claimed in claim 3 in which the substituents R² attached to the 2-, 4- and 5-positions of the tetrahydrofuran nucleus are each hydrogen and the substituents R² attached to the nitrogen atom are identical or different and are selected from hydrogen and alkyl of 1 to 4 carbon atoms. 15

20 5. A dietherified 2,5 - dihydroxy - 3 - aminomethyl - tetrahydrofuran identified in any of the foregoing Examples 1 to 5. 20

6. A process for the manufacture of a di-etherified 2,5 - dihydroxy - 3 - aminomethyl - tetrahydrofuran as claimed in claim 1 wherein a di-etherified 2,5 - dihydroxy - 3 - formyl - tetrahydrofuran of the formula



25 where R¹ and R² have the meanings given in claim 1, is reacted with ammonia or an amine of the formula 25



30 where R² has the above meaning, and hydrogen, in the presence of a hydrogenation catalyst. 30

7. A process as claimed in claim 6, wherein the reaction is carried out with from 1 to 12 moles of starting material III per mole of starting material II. 30

8. A process as claimed in claim 6 or 7, wherein the reaction is carried out at from 30 to 200°C.

9. A process as claimed in claim 6 or 7, wherein the reaction is carried out at from 60 to 100°C.

35 10. A process as claimed in claim 6 or 7, wherein the reaction is carried out at from 70 to 90°C. 35

11. A process as claimed in any of claims 6 to 10, wherein the reaction is carried out at from 10 to 350 bars.

40 12. A process as claimed in any of claims 6 to 11, wherein the reaction is carried out in the presence of a solvent which is inert under the reaction conditions, in an amount of from 30 to 10,000 per cent by weight, based on starting material II. 40

45 13. A process as claimed in any of claims 6 to 12, wherein the reaction is carried out with from 0.5 to 50 per cent by weight, based on starting material II, of a cobalt catalyst or nickel catalyst which optionally contains up to 30 per cent by weight of copper, manganese, iron and/or chromium. 45

14. A process as claimed in any of claims 6 to 13, wherein the reaction is carried out with from 1 to 1,000 moles of H_2 , per mole of starting material II.

15. A process as claimed in any of claims 6 to 14, wherein the substituents R^1 and R^2 in the starting materials II and III have the meanings given in claim 2, 3 or 4.

16. A process for the manufacture of a dietherified 2,5 - dihydroxy - 3 - aminomethyl - tetrahydrofuran claimed in claim 1 carried out substantially as described in any of the foregoing Examples.

17. A dietherified 2,5 - dihydroxy - 3 - aminomethyl - tetrahydrofuran when manufactured by a process as claimed in any of claims 6 to 16.

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