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# PATENT SPECIFICATION

(11) 1 586 793

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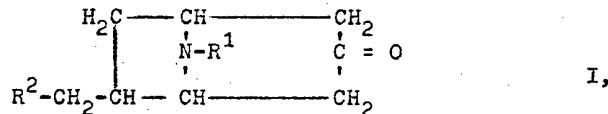
## (54) NEW 6-SUBSTITUTED TROPINONES AND THEIR MANUFACTURE

(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:—

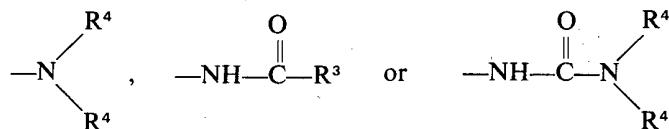
The present invention relates to 6-substituted tropinones and to a process for their manufacture.

British Patent 791,770 discloses that succindialdehyde can be reacted with acetonedicarboxylic acid and methylamine to give tropinone. The reaction is carried out at from 55 to 60°C. Instead of pure succindialdehyde, the reaction mixture obtained by manufacturing this compound by hydrolysis of 2,5-dimethoxytetrahydrofuran in dilute hydrochloric acid is used. Preferably the reaction is carried out at a pH of from 5 to 5.4, with the 3 starting materials being employed in the ratio of 1.25 mole of acetonedicarboxylic acid to 1.25 mole of methylamine to 1 mole of 2,5-dimethoxytetrahydrofuran.

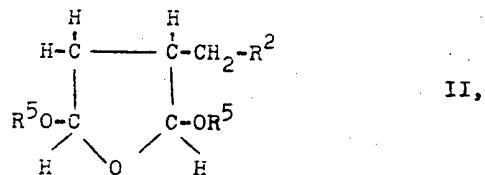
We have found that 6-substituted tropinones of the formula



where  $\text{R}^1$  is an aliphatic radical,  $\text{R}^2$  is  $-\text{OR}^3$ ,



the individual radicals  $\text{R}^4$  are identical or different and each of them and  $\text{R}^3$  are hydrogen or an aliphatic, araliphatic or aromatic radical, and two radicals  $\text{R}^4$  together with the adjacent nitrogen may alternatively form a heterocyclic ring, are obtained in an advantageous manner when water is contacted with a dietherified 2,5-dihydroxy-tetrahydrofuran of the formula



where  $\text{R}^2$  has the above meaning and the individual radicals  $\text{R}^5$  are identical or different and each is an aliphatic radical, whilst maintaining a pH of from 0 to 3, and the resulting mixture is reacted, in a second step, with a primary amine of the formula

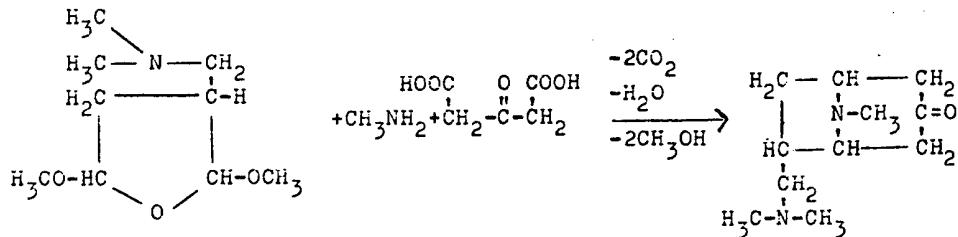
$R^1-NH_2$ 

III,

where  $R^1$  has the above meaning, and with acetonedicarboxylic acid, at a pH of from 4 to 6.

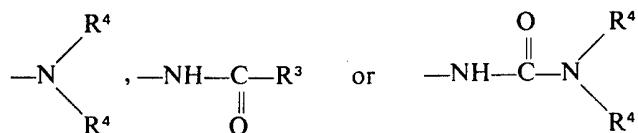
The 6-substituted tropinones of the formula I above are new compounds.

If methylamine and 2,5 - dimethoxy - 3 - (dimethylaminomethyl) - tetrahydrofuran are used, the reaction can be represented by the following equation:



Compared to the prior art, the process of the invention is able to give the new 6-substituted tropinones, which may or may not also be 8-substituted, in a simple and economical manner and in better yield and greater purity. All these advantages of the process of the invention are surprising in view of the prior art. W. Hückel, Theoretische Grundlagen der Organischen Chemie, 8th edition, volume 2, page 758 (Akad. Verlagsgesellschaft Geest & Portig KG, Leipzig 1957) teaches that chain branching has an influence on a cyclizing reaction. Page 764, table 4 of this publication shows that  $\beta,\delta,\delta$ -trimethylvalerolactone has a substantially greater tendency to cyclize than  $\gamma,\delta,\delta$ -trimethylvalerolactone and even more so than  $\delta$ -methyl -  $\delta$  - ethylvalerolactone. It would therefore have been assumed that the 3-substituted starting materials II can only be split to an insignificant degree, if at all, and that therefore no reaction would take place. At the pH of the reaction solution, the amino group of the appropriate starting materials II is at least partially satisified. However, it is known that amine salts catalyse condensations of carbonyl groups with active methylene groups (org. Synth., Coll. Vol. 4, pages 234, 408 and 463 (1963)). Condensations between the methylene groups in the 3-position on the tetrahydrofuran ring with the aldehyde groups of split tetrahydrofuran molecules, and condensations of the split tetrahydrofuran molecules with one another, and, overall, a great reduction in yield, and the formation of heterogeneous mixtures of numerous components and secondary products of the above side-reactions, would therefore have been expected.

The starting materials can be used in the stoichiometric amount, or with either material in excess, preferably with from 1 to 5, especially from 1.1 to 3, moles of starting material III per mole of starting material II and with from 1 to 5, especially from 1.1 to 3, moles of acetonedicarboxylic acid per mole of starting material II. Preferred starting materials II and III and, accordingly preferred end products I are those where  $R^1$  is alkyl of 1 to 6 carbon atoms,  $R^2$  is  $-OR^3$ ,



the individual radicals  $R^3$  and  $R^4$  are identical or different and each is hydrogen, alkyl of 1 to 6 carbon atoms, aralkyl of 7 to 12 carbon atoms or phenyl, and furthermore the two radicals  $R^4$  together with the adjacent nitrogen atom may form a 5-membered or 6-membered heterocyclic ring, which in addition to the said nitrogen atom may contain a further nitrogen atom or an oxygen atom. The above radicals and rings may furthermore be substituted by one or more groups and/or atoms which are inert under the reaction conditions, e.g. alkyl of 1 to 4 carbon atoms or chlorine.

Example of starting materials II are 3 - hydroxymethyl - , 3 - (methoxy - methyl) - , 3 - (ethoxymethyl) - , 3 - (n - propoxymethyl) - , 3 - (isopropoxy - methyl) - , 3 - (n - butoxymethyl) - , 3 - (sec. - butoxymethyl) - , 3 - (isobutoxymethyl) - , 3 - (tert. - butoxymethyl) - , 3 - (benzoxymethyl) - and 3 -

(phenoxyethyl) - 2,5 - dimethoxy - tetrahydrofuran; 3 - (aminomethyl) - , 3 - (N - methylaminomethyl) - , 3 - (N - ethylaminomethyl) - , 3 - (N - n - propylaminomethyl) - , 3 - (N - isopropylaminomethyl) - , 3 - (N - n - butylaminomethyl) - , 3 - (N - sec. - butylaminomethyl) - , 3 - (N - isobutylaminomethyl) - , 3 - (N - tert. - butylaminomethyl) - , 3 - (N - benzylaminomethyl) - , 3 - (N - phenylaminomethyl) - , 3 - (N,N - dimethylaminomethyl) - , 3 - (N,N - diethylaminomethyl) - , 3 - (N,N - di - n - propylaminomethyl) - , 3 - (N,N - diisopropylaminomethyl) - , 3 - (N,N - di - n - butylaminomethyl) - , 3 - (N,N - di - sec. - butylaminomethyl) - , 3 - (N,N - diisobutylaminomethyl) - , 3 - (N,N - di - tert. - butylaminomethyl) - , 3 - (N,N - dibenzylaminomethyl) - , 3 - (N,N - di - phenylaminomethyl) - , 3 - (methylcarboxamidomethyl) - , 3 - (ethylcarboxamidomethyl) - , 3 - (n - butylcarboxamidomethyl) - , 3 - (isobutylcarboxamidomethyl) - , 3 - (sec. - butylcarboxamidomethyl) - , 3 - (tert. - butylcarboxamidomethyl) - , 3 - (benzylcarboxamidomethyl) - , 3 - (phenylcarboxamidomethyl) - , 3 - (N - methylureidomethyl) - , 3 - (N - ethylureidomethyl) - , 3 - (N - n - propylureidomethyl) - , 3 - (N - isopropylureidomethyl) - , 3 - (N - n - butylureidomethyl) - , 3 - (N - isobutylureidomethyl) - , 3 - (N - sec. - butylureidomethyl) - , 3 - (N - tert. - butylureidomethyl) - , 3 - (N - benzylureidomethyl) - , 3 - (N - phenylureidomethyl) - , 3 - (N,N - dimethylureidomethyl) - , 3 - (N,N - diethylureidomethyl) - , 3 - (N,N - di - n - propylureidomethyl) - , 3 - (N,N - diisopropylureidomethyl) - , 3 - (N,N - di - n - butylureidomethyl) - , 3 - (N,N - diisobutylureidomethyl) - , 3 - (N,N - di - sec. - butylureidomethyl) - , 3 - (N,N - di - tert. - butylureidomethyl) - , 3 - (N,N - dibenzylureidomethyl) - , and 3 - (N,N - diphenylureidomethyl) - 2,5 - dimethoxytetrahydrofuran; 3 - (aminomethyl) - and 3 - (ureidomethyl) - 2,5 - dimethoxy - tetrahydrofurans which have two different substituents from amongst those present in the above compounds; 3 - (piperidinyl - (N) - methyl) - , 3 - (piperidinyl - (N) - carboxamidomethyl) - , 3 - (morpholinyl - (N) - methyl) - , 3 - (piperazinyl - (N) - methyl) - , 3 - (morpholinyl - (N) - carboxamidomethyl) - and 3 - (piperazinyl - (N) - carboxamidomethyl) - 2,5 - dimethoxy - tetrahydrofuran; and correspondingly substituted 2,5 - diethoxy - , 2,5 - dipropoxy - , 2,5 - disoproxy - , 2,5 - dibutoxy - , 2,5 - di - sec. - butoxy - , 2,5 - di - tert. - butoxy - and 2,5 - diisobutoxy - tetrahydrofurans. Certain dietherified 2,5 - dihydroxy - 3 - aminomethyltetrahydrofurans are described and claimed as new compounds in our copending GB Patent Application No. 41601/77 (Serial No. 1586791). Examples of starting materials II are methylamine, ethylamine, n-propylamine, isopropylamine, n-butylamine, isobutylamine, sec. - butylamine and tert. - butylamine.

The process is in general carried out at from 20 to 110°C, the contacting with water preferably being carried out at from 70 to 105°C in the first step, and the reaction in the second step preferably being carried out at from 25 to 70°C, at atmospheric or superatmospheric pressure, continuously or batchwise. For the first step, water is added to starting material I, advantageously in an amount of from 25 to 250, preferably from 50 to 60, moles of water per mole of starting material II. In general, water serves simultaneously as the solvent medium for both steps, but, if appropriate, organic solvents which are inert under the reaction conditions, e.g. dioxane, tetrahydrofuran, glycol, methanol, ethanol or isopropanol, or mixtures of these with one another or with water, may also be used. The organic solvent or mixture of the organic solvent with water may be used in an amount of from 10 to 500, preferably from 100 to 200, per cent by weight, based on starting material II.

During the contacting with water prior to the second step a pH of from 0 to 3, preferably from 0.5 to 2.5, is maintained. To adjust the pH, an appropriate amount of acid, which may be inorganic or organic, is added. Instead of monobasic acids, equivalent amounts of polybasic acids may be used. Examples of suitable acids are benzenesulfonic acid, toluenesulfonic acids, formic acid, acetic acid, propionic acid, hydrochloric acid, hydrobromic acid, hydriodic acid, perchloric acid, sulfuric acid, nitrous acid, phosphoric acid and nitric acid. Sulfuric acid and especially hydrochloric acid are preferred.

In the second step, a pH of from 4 to 6, preferably from 5.0 to 5.5, is maintained. To adjust the pH, a basic compound is used, preferably a tertiary amine, an alkaline earth metal compound, an ammonium compound or, especially, an alkali metal compound, or a mixture of two or more of these. Advantageous alkali metal compounds and alkaline earth metal compounds to use are the hydroxides, oxides, carbonates, bicarbonates and salts with weak or polybasic acids

of calcium, barium, magnesium, lithium and especially sodium and potassium. Examples of suitable basic compounds are potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, barium oxide, magnesium hydroxide, calcium carbonate and sodium acetate. Potassium hydroxide and sodium hydroxide are particularly preferred. Another possibility is to add the primary amine III, as a salt or as the free base, where appropriate in excess, and thus to adjust the pH together with one of the above basic compounds; the amine III may replace some or all of one of the above basic compounds.

The process may be carried out as follows: a mixture of the starting material II, acid and water is kept for from 0.1 to 5 hours, preferably from 0.25 to 2 hours, at the temperature and the pH mentioned above for the contacting with water. It is then brought to the pH used for the second step by means of a base, the starting material III and acetonedicarboxylic acid are added and the mixture is kept for from 0.5 to 10, preferably from 1 to 6, hours at the reaction temperature and the pH used for the second step. The end product is then isolated from the mixture by conventional methods, e.g. by bringing the mixture to a pH of from 8 to 12 with a base, extracting it, for example with ether, and subjecting the extract to fractional distillation.

The 6-substituted tropinones obtainable by the process of the invention are interesting starting materials for the manufacture of dyes, plant protection agents and especially drugs, e.g. drugs having a spasmolytic action. By reduction with hydrogen in the presence of a nickel catalyst, e.g. by the process of U.S. Patent 2,366,760, 6-substituted tropines are obtained, which may be converted into 6-substituted atropines by esterification with acetyl tropic acid chloride, for example by the method disclosed in *Chemische Berichte*, 41, (1908), 730—732. Atropine and its derivatives are important spasmolytics (Kuchinsky and H. Lüllmann, *Kurzes Lehrbuch der Pharmakologie*, 6th edition, Stuttgart 1974, pages 11 and 13).

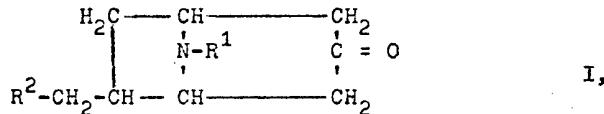
In the example which follows, parts are by weight and bear the same relation to parts by volume as that of the kilogram to the liter.

#### EXAMPLE

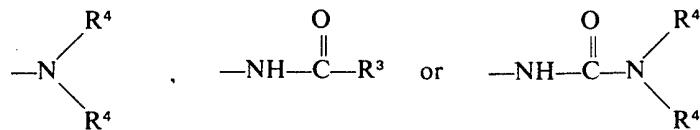
81 parts of 2,5 - dimethoxy - 3 - (dimethylaminomethyl) - tetrahydrofuran are added to 427 parts by volume of 1-normal HCl and 342 parts of volume of water. The solution is heated to 100°C under reflux and the pH is brought to 1.5 with 1-normal HCl. The mixture is then refluxed at pH 1.5 for one hour, after which it is brought to pH 6 with 1-normal sodium hydroxide solution. The resulting solution is then added, in the course of 30 minutes, to a mixture of 148 parts of acetonedicarboxylic acid, 68 parts of methylamine hydrochloride, 171 parts of sodium acetate and 570 parts of water. The mixture is then stirred at pH 5 for 4 hours at 25°C followed by 2 hours at 60°C. When it has cooled to room temperature, 125 parts of potassium carbonate and 171 parts of sodium chloride are added. The mixture is extracted with ether. The combined ether solutions are dried and evaporated. The residue is distilled. 74 parts of 6 - dimethylaminomethyl - 8 - methyl - tropinone (89% of theory), boiling point 150—160°C/ 2 m bars, are obtained.

#### WHAT WE CLAIM IS:

1. A 6-substituted tropinone of the formula

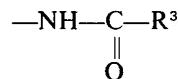


where R<sup>1</sup> is an aliphatic radical, R<sup>2</sup> is —OR<sup>3</sup>,

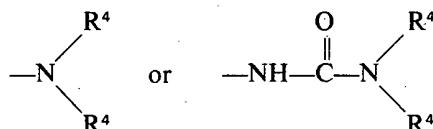


the individual radicals R<sup>4</sup> are identical or different and each of them and R<sup>3</sup> are hydrogen or an aliphatic, araliphatic or aromatic radical, and two radicals R<sup>4</sup> together with the adjacent nitrogen may alternatively form a heterocyclic ring.

2. A 6-substituted tropinone as claimed in claim 1, wherein, in the formula I, R<sup>1</sup> is alkyl of 1 to 6 carbon atoms and R<sup>2</sup> is —OR<sup>3</sup> or



5 (where R<sup>3</sup> is hydrogen, alkyl of 1 to 6 carbon atoms, aralkyl of 7 to 12 carbon atoms or phenyl) or R<sup>2</sup> is

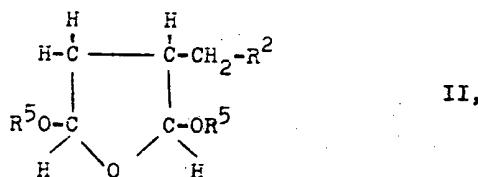


10 (where the radicals R<sup>4</sup> are identical or different and each has the meaning given above for R<sup>4</sup> or the two radicals R<sup>4</sup> together with the adjacent nitrogen atom form a 5-membered or 6-membered heterocyclic ring optionally also containing an oxygen atom or a further nitrogen atom), and any alkyl, aralkyl or phenyl radical or heterocyclic ring is optionally substituted by chlorine or alkyl of 1 to 4 carbon atoms.

10

15 3. 6-Dimethylaminomethyl - 8 - methyl - tropinone.

15 4. A process for the manufacture of a 6-substituted tropinone as claimed in claim 1 or 2, wherein water is contacted with a dietherified 2,5 - dihydroxy - tetrahydrofuran of the formula



20 where R<sup>2</sup> has the meaning given in claim 1 or 2 and the individual radicals R<sup>5</sup> are identical or different and each is an aliphatic radical, whilst maintaining a pH of from 0 to 3, and the resulting mixture is reacted, in a second step, with a primary amine of the formula



25 where R<sup>1</sup> has the meaning given in claim 1 or 2, and with acetonedicarboxylic acid, at a pH of from 4 to 6.

25

25 5. A process as claimed in claim 4, which is carried out with from 1 to 5 moles of starting material III and from 1 to 5 moles of acetonedicarboxylic acid per mole of starting material II.

30 6. A process as claimed in claim 4 or 5, which is carried out at from 20 to 110°C.

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7. A process as claimed in claim 4 or 5, in which the contacting with water is carried out at from 70 to 105°C.

30

8. A process as claimed in claim 4 or 5, in which the reaction in the second step is carried out at from 25 to 70°C.

35 9. A process as claimed in any of claims 4 to 8, in which from 25 to 250 moles of water are added per mole of starting material II.

35

10. A process as claimed in any of claims 4 to 9, in which during the contacting with water before the second step the pH is maintained at from 0.5 to 2.5.

11. A process as claimed in any of claims 4 to 10, in which the reaction in the second step is carried out at a pH of from 5.0 to 5.5.

40 12. A process as claimed in any of claims 4 to 11, in which a mixture of compound II and water is kept for a period of from 0.1 to 5 hours and in the second step the reaction is carried out for from 0.5 to 10 hours.

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13. A process as claimed in any of claims 4 to 12, wherein a starting material II individually named herein and a starting material III individually named herein, are employed.

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14. A process for the manufacture of a 6-substituted tropinone carried out substantially as described in the foregoing Example.

15. A 6-substituted tropinone when manufactured by a process as claimed in any of claims 4 to 14.

5 16. A 6-substituted tropine when obtained from a 6-substituted tropinone claimed in claim 1, 2, 3 or 15 by reduction with hydrogen in the presence of a nickel catalyst.

17. A 6-substituted atropine when obtained from a 6-substituted tropine claimed in claim 16 by esterification with acetyl tropic acid chloride.

10 18. Dyes, plant protection agents and drugs when obtained from a 6-substituted tropinone claimed in claim 1, 2, 3 or 15.

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