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PATENT SPECIFICATION

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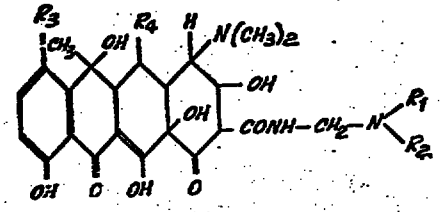
COMPLETE SPECIFICATION

Water-Soluble Tetracycline Derivatives and process for their Manufacture

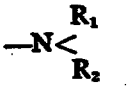
We, FARBWERKE HOECHST AKTIENGESELLSCHAFT vormals Meister Lucius & Brüning, a body corporate recognised under German law, of Frankfurt (M)—Hoechst, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The tetracyclines, for example, tetracycline, oxytetracycline and chlorotetracycline are sparingly soluble in water over a wide range of pH values. For the preparation of aqueous solutions for pharmaceutical purposes there have hitherto been used salts of the tetracyclines. As these salts are stable in solution only at extreme pH values it is difficult to administer them, for example, by intramuscular injection. Their occasionally poor local tolerability is due principally to the precipitation of tetracyclines from solutions thereof in buffered tissue fluids. Attempts have been made to overcome these difficulties, for example, in the intramuscular injection of tetracyclines, by adding local anaesthetics (see Specification No. 793,558 and Belgian Patent No. 539,034). Thus, in order to stabilize such solutions, there have been added organic acids, for example, ascorbic acid or citric acid, or magnesium chloride. The low pH-values of the solutions of tetracyclines (see Specification No. 768,735) also makes it difficult to use these highly active antibiotics over a wide range of applications.

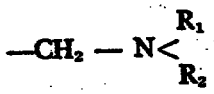
The present invention provides amino-methylation products of tetracycline, chloro-tetracycline and hydroxy-tetracycline in their anti-bacterial isomeric forms, which products correspond to the presumed general formula



in which R_1 represents hydrogen or an alkyl group containing 1 to 8 carbon atoms, a cycloalkyl, a hydroxyalkyl or a diethylaminoethyl group, R_2 represents hydrogen or an alkyl group containing 1 to 8 carbon atoms, a cycloalkyl or a hydroxyalkyl group, or

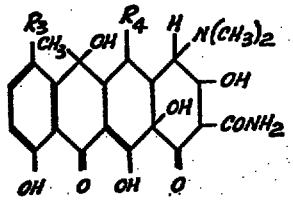


represents the radical of a heterocyclic amine, R_3 represents hydrogen or chlorine, and R_4 represents hydrogen or where R_3 is hydrogen, R_4 is hydrogen or a hydroxyl group, and also physiologically tolerable aminomethylation products of anhydro-tetracycline in its anti-bacterial isomeric forms in which the amino-methyl group corresponds to the formula



where R_1 and R_2 have the meanings given above, and physiologically tolerable acid addition salts of these compounds.

The invention also provides a process for the manufacture of water-soluble amino-methylation products of the tetracyclines as defined above, wherein an anti-bacterial isomeric form of tetracycline, chloro-tetracycline or hydroxy-tetracycline corresponding to the general formula



in which R_3 and R_4 have the meanings given above, or an anti-bacterial isomeric form of anhydro-tetracycline, is amino-methylated

[*Price 3s. 6d.*]

(Mannich reaction) so as to introduce the aminomethyl radical.

$$-CH_2-N<^{R_1}_{R_2}$$

in which R_1 and R_2 have the meanings given above. The aminomethylation may be carried out, for example, by reaction with formaldehyde and ammonia or an amine capable of bringing about aminomethylation (Mannich reaction; cf. Organic Reactions 1942, I, pages 303—341; Angewandte Chemie 1956, volume 68, page 265 et seq.).

The compounds of this invention, in the form of the free bases and of salts thereof, are new and possess an excellent solubility in water over a wide range of pH values, and they exhibit the full biological activity of the tetracyclines from which they are derived and are therefore of considerable value in medicine. Owing to their excellent solubility in water they are suitable for making preparations which can be administered orally or by intramuscular or intravenous injection, and which can be adjusted to a neutral pH value. When these compounds are used precipitation of the sparingly soluble free bases of the tetracyclines, which occurs with the known tetracycline preparations, is completely avoided, whereby their tolerability and absorption are considerably improved. This leads rapidly to high blood level values.

For making the new compounds from the said tetracyclines, the antibiotics may be used in the form of their free bases or as salts with inorganic or organic acids or with inorganic or organic bases.

The formaldehyde required for the aminomethylation may be used in the form of an aqueous solution of formaldehyde or of a solution of formaldehyde in an organic hydrous or anhydrous solvent, or in the gaseous or solid (polymeric) form.

Alternatively, there may be used a substance capable of yielding formaldehyde under the conditions of aminomethylation, for example, chloromethyl methyl ether.

As amines may be used for the reactions: ammonia or primary or secondary aliphatic or heterocyclic amines, for example, methylamine, ethylamine, n-butylamine, cyclohexylamine, octadecylamine, dimethylamine, diethylamine, di - n - butylamine, diisobutylamine, di-isohexylamine, N-methyl-octadecylamine, ethanolamine, diethanolamine, diethylamino-ethylamine, di - (diethylaminoethyl)-amine, piperidine, pyrrolidine, morpholine, piperazine or N-methyl-piperazine. There may be used any amines suitable for the aminomethylation.

The amines may be used as the free bases or as salts thereof with inorganic or organic acids, and in the latter case the corresponding salts of the aminomethylated tetracyclines are obtained.

The salts of the aminomethylated tetracyclines can also be obtained by reacting acid salts of the tetracyclines with free amines and formaldehyde, or by adding acids before, during or after the reaction of the free tetracyclines with the free bases and formaldehyde.

The free aminomethylated tetracyclines are obtained by reacting the free tetracyclines with the free amine bases and formaldehyde.

For making salts of the aminomethylated tetracyclines there may be used a very wide variety of acids, for example, carbonic acid, hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, palmitic acid, oleic acid, lactic acid, tartaric acid, citric acid, gluconic acid, ascorbic acid or panthothenic acid, or penicillins.

The aminomethylation reaction used in the process of this invention includes the so-called transaminomethylation reaction, that is to say, the compounds may be prepared by reaction of the tetracyclines with aminomethyl-compounds capable of introducing the aminomethyl radical

$$-CH_2-N<^{R_1}_{R_2}$$

as defined above into the tetracycline. There are especially suitable aminomethyl-compounds of hydrogen halides, water, alcohols, hydrogen sulphite ion, phthalimide, succinimide, piperidine, pyrrolidine, morpholine, alkyl malonic acid esters or acylamino-malonic esters, the amine portions of these aminomethyl-compounds being those of the amines mentioned above. As such compounds there may be mentioned N-morpholino-methyl succinimide and N-chloro-methyl-morpholine.

As solvents in which the aminomethylation of the tetracyclines may be carried out there are used water or aqueous or non-aqueous organic solvents. There may be used alcohols containing 1 to 6 carbon atoms, ethyl acetate, tetrahydrofurane, dioxane, pyridine, glacial acetic acid, dimethylformamide, methylene chloride, chloroform or benzene.

The reactions may be carried out at temperatures within the range of −15°C to +80°C, and advantageously, 0°C to +20°C.

The yields of the compounds of the invention are on the average 90% of the theoretical yield.

The following Examples illustrate the invention:—

EXAMPLE 1

Piperidinomethyl-tetracycline acetate

44.3 Grams of tetracycline (base) (=0.1 mol) are dissolved in 1000 cc of tetrahydrofurane. At a temperature of +15°C there are added to the solution, while stirring, 14.5 grams of piperidine acetate (0.1 mol) and 13.8 cc of a formalin solution of 36.7%

strength (0.125 mol). After a few seconds precipitation sets in. The stirring is continued for 2 hours until the reaction is complete. The light yellow precipitate that has formed is filtered off with suction and washed with tetrahydrofurane. The piperidinomethyl-tetracycline acetate thus obtained is finally freed from the adhering solvent under reduced pressure at about 40°C.

The yield amounts to 55.0 grams (=91.5% of the theoretical yield). There are obtained light yellow crystals melting at 143—145°C (with decomposition).

Composition:

$C_{30}H_{39}O_{10}N_3$ (molecular weight 601.3)

Calculated: C=59.87%, H=6.53%, O=26.61%, N= 6.98%

Found: C=60.12%, H=6.29%, O=26.58%, N= 7.22%

Example 2

Morpholinomethyl-tetracycline hydrochloride.

(a) To a solution of 48.0 grams of tetracycline hydrochloride (0.1 mol) in 1000 cc of methanol there are added at room temperature, while stirring, 11.0 cc of a formaldehyde solution (36.7% strength (0.1 mol) and 8.7 grams of morpholine (0.1 mol). After stirring for 2 hours the reaction is complete. The light yellow precipitate of morpholinomethyl-tetracycline hydrochloride that has formed is isolated, washed with methanol, and dried at 40°C under reduced pressure.

The yield amounts to 53.4 grams (=92.3% of the theoretical yield). There are obtained light yellow crystals decomposing above 165°C.

Composition:

$C_{27}H_{34}O_9N_3Cl$ (molecular weight 579.7)

Calculated: C=55.89%, H=5.91%, O=24.84%, N= 7.25% Cl=6.12%

Found: C=55.73%, H=5.82%, O=24.91%, N= 7.20%, Cl=6.38%.

(b) 8.0 grams of chloromethyl methyl ether (0.1 mol) are introduced dropwise at +15°C, while stirring, into a solution of 8.7 grams of morpholine (0.1 mol) and 44.3 grams of tetracycline (base) (0.1 mol) in 800 cc of tetrahydrofurane. After stirring for 2 hours the light yellow precipitate of morpholinomethyl-tetracycline hydrochloride that has formed is isolated, washed with a little cold tetrahydrofurane and ether, and dried at 40°C under reduced pressure. A further quantity of the reaction product can be isolated by concentrating the mother liquor. The yield amounts to 51.0 grams (=88% of the theoretical yield).

(c) 2.0 Grams of N-morpholinomethyl succinimide (0.01 mol) and 4.8 grams of tetracycline hydrochloride (0.01 mol) are dissolved, while stirring, in 75 cc of methanol. After standing for 1 hour at 20°C the reaction mixture contained in the flask solidifies. It is then intimately stirred with 350 cc of dry ether. The light yellow precipitate of morpholinomethyl tetracycline hydrochloride is isolated, and washed well with ether in order to remove completely the adhering succinimide. The reaction product is dried at 40°C under reduced pressure. The yield amounts to 5.3 grams (=91% of the theoretical yield).

(d) A solution of 1.35 grams of N-chloromethylmorpholine in 20 cc of dimethylformamide is added dropwise at 5°C, while stirring, to a solution of 4.4 grams of the tetracycline base (0.01 mol) in 25 cc of dimethylformamide. After standing for 2 hours the reaction mixture solidifies. It is then stirred well with 400 cc of dry ether. The light yellow precipitate is isolated and washed with ether.

The morpholinomethyl tetracycline hydrochloride thus obtained is dried at 40°C under reduced pressure. The yield amounts to 5.0 grams (=86% of the theoretical yield).

The compounds obtained as described under (b), (c) and (d) are identical, and correspond in their properties to the morpholinomethyl-tetracycline hydrochloride obtained as described in Example 2(a).

Example 3

Pyrrolidinomethyl-oxytetracycline formate

To 7.1 grams of pyrrolidine (0.1 mol) in 50 cc of methanol are added 13.8 cc of a formaldehyde solution of 36.7% strength (0.125 mol). The solution is allowed to stand for 15 minutes, and is then added at room temperature to a solution of 45.9 grams of oxytetracycline base (0.1 mol) and 4.6 grams of formic acid (0.1 mol) in 5 litres of methanol. The reaction mixture is then allowed to stand for 8 hours in the refrigerator. After concentrating the solution under reduced pressure the light yellow precipitate of pyrrolidinomethyl-oxytetracycline formate that has formed is isolated, washed with a little methanol, and dried at 40°C under reduced

pressure. A further quantity of the formate is obtained by concentrating the mother liquor.

The yield amounts to 57.0 grams (=96.9% of the theoretical yield). The crystals obtained decompose above 155°C.

Composition:

$C_{28}H_{35}O_{11}N_3$ (molecular weight 589.3)
Calculated: C=57.02%, H=5.98%, O=29.87%, N= 7.13%
Found: C=57.29%, H=5.67%, O=29.90%, N= 7.32%

Example 4

N-methylpiperazino-methyl-chlorotetracycline diacetate

In 2 litres of methanol there are dissolved at room temperature 47.8 grams of chlorotetracycline (0.1 mol), 13.8 cc of a formaldehyde solution of 36.7% strength (0.125 mol) and 22.0 grams of N-methylpiperazine diacetate (0.1 mol). The reaction mixture is allowed to stand for 8 hours in the refrigerator, and is then concentrated under reduced pressure until the N-methylpiperazinomethyl-chlorotetracycline diacetate separates. The light yellow precipitate so obtained is isolated, washed with methanol, and dried under reduced pressure at 40°C.

A further quantity of the product is obtained by concentrating the mother liquor.

The yield amounts to 64.5 grams (=90.8% of the theoretical yield).

The substance changes colour when heated above 120°C and decomposes above 160°C.

Composition:

$C_{32}H_{43}O_{12}N_4Cl$ (molecular weight 710.8)
Calculated: C=54.02%, H=6.09%, O=27.01%, N= 7.88%, Cl=5.00%
Found: C=54.35%, H=5.84%, O=27.22%, N= 8.03%, Cl=4.79%.

Example 5

Piperidinomethyl-anhydrotetracycline acetate

A mixture of 40 cc of tetrahydrofurane, 13.8 cc of a formaldehyde solution of 36.7% strength (0.125 mol) and 8.5 grams of piperidine (0.1 mol) is prepared and allowed to stand for 15 minutes. The mixture is then added to a solution of 42.5 grams of anhydrotetracycline (0.1 mol) and 6.0 cc of glacial acetic acid (0.1 mol) in 500 cc of tetrahydrofurane. After allowing the mixture to stand for 2 hours in the refrigerator, the yellow crystalline precipitate of piperidinomethyl-anhydrotetracycline acetate has formed it is isolated, washed with tetrahydrofurane, and dried at 40°C under reduced pressure.

The yield amounts to 52.7 grams (=90.5% of the theoretical yield). The product decomposes slowly when heated to temperatures above 120°C.

Composition:

$C_{30}H_{37}O_9N_3$ (molecular weight 585.3)
Calculated: C=61.72%, H=6.30%, O=24.69%, N= 7.20%
Found: C=61.98%, H=5.99%, O=24.84%, N= 7.33%.

Example 6

Ethanolaminoethyl-tetracycline acetate

Into a mixture of 400 cc of methanol, 6.1 grams of ethanolamine (0.1 mol), 6.0 cc of glacial acetic acid (0.1 mol) and 14.3 cc of a methanolic formaldehyde solution (of 21.1% strength) (0.1 mol) are introduced at room temperature, while stirring, 44.3 grams of tetracycline (base) (0.1 mol). After stirring the whole for 2 hours the reaction is complete. The clear solution concentrated at room temperature under reduced pressure and introduced into 2000 cc of dry ether. The light yellow precipitate of ethanolaminomethyl-tetracycline acetate that has formed is isolated and washed with dry ether. The product can be dried at 40°C under reduced pressure. The yield amounts to 51.8 grams (89.8% of the theoretical yield). The light yellow powder decomposes above 140°C.

ethanolamino

Composition:

$C_{27}H_{35}O_{11}N_3$ (molecular weight 577.3)
Calculated: C=56.12%, H=6.11%, O=30.49%, N= 7.28%
Found: C=56.01%, H=6.34%, O=30.68%, N= 7.01%.

EXAMPLE 7

Diethanolaminomethyl-tetracycline ascorbate

3.0 Grams of gaseous formaldehyde are introduced at +10°C into a mixture of 400 cc of methanol, 10.5 grams of diethanolamine (0.1 mol), 17.6 grams of ascorbic acid (0.1 mol) and 44.3 grams of tetracycline (base) (0.1 mol). After standing for 1 hour the reaction solution is concentrated under reduced pressure at room temperature and introduced into 2000 cc of dry ether. A light yellow precipitate of diethanolaminomethyl-tetracycline ascorbate separates which is then isolated and washed with ether. The reaction product can be freed from the adhering solvent at 40°C under reduced pressure. The yield amounts to 68.2 grams (=92.5% of the theoretical yield). The light yellow crystals decompose above 98°C.

Composition:

$C_{33}H_{43}O_{16}N_3$ (molecular weight 737.4)
Calculated: C=53.71%, H=5.88%, O=34.72%, N= 5.70%
Found: C=54.00%, H=5.91%, O=34.56%, N= 5.88%.

EXAMPLE 8

N-(Diethylaminoethyl)-aminomethyl-tetracycline diacetate

400 cc of methanol, 11.6 grams of diethylamino-ethylamine (0.1 mol), 12.0 cc of glacial acetic acid (0.2 mol) and 14.3 cc of a methanolic formaldehyde solution (of 21.1% strength) (0.1 mol) are mixed together. 44.3 Grams of tetracycline (base) (0.1 mol) are added at room temperature over a period of 1½ hours, while stirring, to the solution obtained. The clear solution is stirred for a further 30 minutes and concentrated at 20°C under reduced pressure. By precipitation with ether (2000 cc) N-(diethylaminoethyl)-aminomethyl-tetracycline disacetate is obtained as a microcrystalline yellow powder. It is washed with ether and dried at 40°C under reduced pressure. The yield amounts to 61.2 grams (88.4% of the theoretical yield). The reaction product decomposes above 120°C.

Composition:

$C_{32}H_{48}O_{12}N_4$ (molecular weight 692.4)
Calculated: C=57.19%, H=6.99%, O=27.73%, N= 8.09%
Found: C=57.34%, H=7.20%, O=27.76%, N= 8.34%.

EXAMPLE 9

Piperidinomethyl-tetracycline penicillin G salt

(a) Piperidinomethyl-tetracycline:

In 300 cc of methanol are dissolved at room temperature 13.0 grams of N-methoxy-methylpiperidine (0.1 mol) and 44.3 grams of tetracycline (base) (0.1 mol). After standing for 2 hours the clear solution is concentrated under nitrogen and under reduced pressure, and is introduced into 1000 cc of dry ether. The light yellow precipitate of piperidinomethyl-tetracycline thus obtained is isolated, washed with ether and dried at 40°C under reduced pressure. The yield amounts to 4.93 grams (91.2% of the theoretical yield). The product dissolves easily in water, methanol, tetrahydrofurane, chloroform, glacial acetic acid and pyridine. It decomposes above 155°C.

Composition:

$C_{28}H_{35}O_8N_3$ (molecular weight 541.3)
Calculated C=62.08%, H=6.53%, O=23.65%, N= 7.76%
Found: C=61.99%, H=6.40%, O=23.53%, N= 7.95%.

(b) Piperidinomethyl-tetracycline penicillin G salt:

5.4 Grams of piperidinomethyl-tetracycline (0.01 mol) are dissolved in 75 cc of water. An ethereal solution of 3.3 grams of penicillin G (0.01 mol) is added to the solution at 5°C, and the whole is shaken vigorously. The aqueous phase is separated and lyophilized. The light yellow piperidinomethyl-tetracycline penicillin G salt is obtained in a yield of 8.5 grams (=96.8% of the theoretical yield). It decomposes above 139°C.

Composition:

$C_{44}H_{53}O_{12}N_5S$ (molecular weight 875.5)

Calculated: C=60.30%, H=6.10%, O=21.93%, N= 8.00%, S=3.67%

Found: C=60.09%, H=6.12%, O=22.03%, N= 8.22%, S=3.96%.

EXAMPLE 10

Pyrrolidino-methyl-tetracycline pantothenate

(a) Pyrrolidinomethyl-tetracycline:

710 milligrams of pyrrolidine and 1.4 cc of a formaldehyde solution (0.01 mol) of 36.7% strength are dissolved in 350 cc of water. Into the solution are introduced at 15°C, while stirring, 5.0 grams of tetracycline trihydrate (base) (0.01 mol). The solution which becomes clear very soon is allowed to stand for 30 minutes under nitrogen. Lyophilization yields pyrrolidinomethyl-tetracycline. The light yellow product decomposes above 156°C. The yield amounts to 5 grams (=95% of the theoretical yield).

Composition:

$C_{27}H_{33}O_8N_3$ (molecular weight 527.3)

Calculated: C=61.45%, H=6.31%, O=24.27%, N= 7.97%

Found: C=61.71%, H=6.09%, O=24.23%, N= 8.16%.

(b) Pyrrolidinomethyl-tetracycline pantothenate:

5.3 Grams of pyrrolidinomethyl-tetracycline (0.01 mol) are dissolved in 30 cc of water, and there are then added 43.8 cc of an aqueous pantothenic acid solution of 5% strength (0.01 mol) (prepared from a sodium pantothenate solution by means of a cation exchanger). Lyophilization yields the light yellow pyrrolidinomethyl-tetracycline pantothenate. It decomposes above 122°C. The yield amounts to 7.3 grams (=97.3% of the theoretical yield).

Composition:

$C_{36}H_{50}O_{13}N_4$ (molecular weight 746.4)

Calculated: C=57.88%, H=6.75%, O=27.86%, N= 7.51%

Found: C=57.94%, H=6.51%, O=27.77%, N= 7.70%.

EXAMPLE 11

Diethylaminomethyl-tetracycline

10.8 Grams of diethyl-oxymethylamine (of 95% strength) (0.1 mol) and 44.3 grams of tetracycline (base) (0.1 mol) are introduced at −10°C into 350 cc of methanol. The reaction mixture is stirred for one hour. The solution is concentrated under reduced pressure and introduced into 1500 cc of dry ether, whereupon the light yellow diethylaminomethyl-tetracycline separates. The precipitate is isolated, washed with ether and dried at 40°C under reduced pressure. The yield amounts to 44.3 grams (=83.7% of the theoretical yield). The product decomposes above 158°C.

Composition:

$C_{27}H_{35}O_8N_3$ (molecular weight 529.3)

Calculated: C=61.22%, H=6.66%, O=24.18%, N= 7.94%

Found: C=61.42%, H=6.86%, O=24.10%, N= 8.21%.

EXAMPLE 12
Aminomethyl-tetracycline

4.6 Grams of tetracycline (ammonium salt) (0.01 mol) are dissolved at 25°C in 100 cc of methanol. To the clear solution are added 1.4 cc of a methanolic formaldehyde solution (of 21.1% strength) (0.01 mol). After about 30 minutes the precipitation of yellow aminomethyl-tetracycline sets in. After 3 hours the precipitate is isolated, and washed with ether. A further quantity of the aminomethyl-tetracycline is obtained by concentrating the mother liquor under reduced pressure. The product is dried at 40°C under reduced pressure. It decomposes slowly above 180°C. The free base, as compared with most of the substituted aminomethyl compounds, is less soluble in water. However, it forms salts with organic acids, for example, with acetic acid, which are easily soluble in water. The yield amounts to 4.0 grams (=85.0% of the theoretical yield).

Composition:

$C_{23}H_{27}O_8N_3$ (molecular weight 473.2)
Calculated: C=58.33%, H=5.75%, O=27.04%, N= 8.88%
Found: C=58.19%, H=5.79%, O=27.26%, N= 8.67%.

EXAMPLE 13
Piperidinomethyl-oxytetracycline acetate

(a) 1.8 Grams of N:N¹-methylene-dipiperidine (0.01 mol) and 4.6 grams of oxytetracycline (base) (0.01 mol) are dissolved at 15°C, while stirring, in 30 cc of glacial acetic acid. After 2 hours the reaction mixture is added, while stirring, to 300 cc of ether. The light yellow precipitate of piperidinomethyl-oxytetracycline acetate is filtered off with suction, washed with ether, and dried at 40°C under reduced pressure. The yield amounts to 5.2 grams (=84% of the theoretical yield). The product decomposes above 135°C.

(b) 0.85 Gram of piperidine (0.01 mol) and 4.6 grams of oxytetracycline (base) (0.01 mol) are dissolved at 35°C, while stirring, in 30 cc of glacial acetic acid. 0.6 Gram of paraformaldehyde (0.02 mol) is added to the solution, and the whole is stirred for 30 minutes. The residual undissolved paraformaldehyde is then separated. The clear filtrate is concentrated under nitrogen and under reduced pressure, and introduced into 100 cc of ether. The light yellow precipitate of piperidinomethyl-oxytetracycline acetate is further treated as described above. The yield amounts to 5.3 grams (=86% of the theoretical yield). The products obtained under (a) and (b) have the same properties.

Composition:

$C_{28}H_{39}O_{11}N_3$ (molecular weight 617.3)
Calculated: C=58.32%, H=6.37%, O=28.51%, N= 6.80%
Found: C=58.60%, H=6.35%, O=28.44%, N= 6.79%.

EXAMPLE 14
Pyrrolidinomethyl-tetracycline

To 120 cc of methylene chloride are added 7.5 cc of pyrrolidine and 6.5 cc of a methanolic solution of formaldehyde (content 48.5% of formaldehyde). The water formed by the reaction is removed by means of sodium sulphate (calcined). To the dried solution are added dropwise in portions, while stirring, 33.6 grams of tetracycline (anhydrous). The suspension first obtained soon becomes a clear, dark yellow solution, which becomes turbid after a further 10—20 minutes. In a short time the crystallization of the pyrrolidinomethyl-tetracycline formed is complete, and the contents of the flask solidify.

There are obtained fine needles, which are often united in clusters. The yield (after drying the product for 24 hours at 60°C in the vacuum) amounts to 29.20 grams (=73% of the theoretical yield).

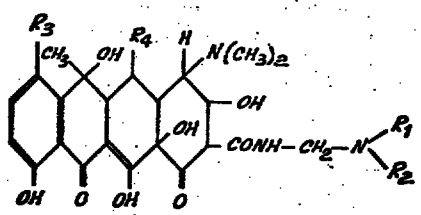
The product has the specific rotation $[\alpha]_D 22°C = -183°C$ (in methanol). It melts at 162—165°C (with decomposition). 1250 milligrams of the product dissolve in 1 cc of water at 18°C.

Composition:

$C_{27}H_{33}O_8N_3$ (molecular weight 527.3)
Calculated: C=61.45%, H=6.31%, O=24.27%, N=7.97%
Found: C=61.71%, H=6.09%, O=24.23%, N=8.16%.

WHAT WE CLAIM IS:—

1. Physiologically tolerable aminomethylation products of tetracycline, chloro-tetracycline and hydroxy-tetracycline in their anti-bacterial isomeric forms, which products correspond to the presumed general formula



in which R_1 represents hydrogen or an alkyl group containing 1 to 8 carbon atoms, a cycloalkyl, a hydroxyalkyl or a diethylaminoethyl group, R_2 represents hydrogen or an alkyl group containing 1 to 8 carbon atoms, a cycloalkyl or a hydroxyalkyl group, or

$$-N<^{R_1}_{R_2}$$

represents the radical of a heterocyclic amine, R_3 represents hydrogen or chlorine, and R_4 represents hydrogen or, where R_3 is hydrogen, R_4 is hydrogen or a hydroxyl group, and also physiologically tolerable aminomethylation products of anhydro-tetracycline in its anti-bacterial isomeric forms in which the aminomethyl group corresponds to the formula

$$-CH_2-N<^{R_1}_{R_2}$$

where R_1 and R_2 have the meanings given above.

2. Addition salts of the compounds claimed in claim 1 with acids yielding physiologically tolerable salts with such compounds.

3. Compounds as claimed in claim 1 or 2, in which

$$-N<^{R_1}_{R_2}$$

represents the pyrrolidino, piperidino, piperazino, methyl-piperazino or morpholino group.

4. Piperidinomethyl-tetracycline or its acetate.

5. Morpholinomethyl-tetracycline or its hydrochloride.

6. Pyrrolidinomethyl-oxytetracycline or its formate.

7. N - Methylpiperazinomethyl - chloro-tetracycline or its ~~diacetate~~.

8. Piperidinomethyl-anhydrotetracycline or its acetate.

9. Ethanolaminomethyl-tetracycline or its acetate.

10. Diethanolaminomethyl-tetracycline or its ascorbate.

11. N - (Diethylaminoethyl) - aminomethyl - tetracycline or its diacetate.

12. Piperidinomethyl-tetracycline penicillin G salt.

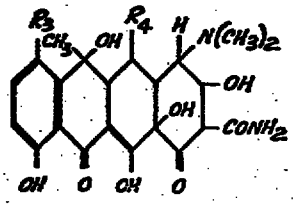
13. Pyrrolidinomethyl-tetracycline or its pantothenate.

14. Diethylaminomethyl-tetracycline.

15. Aminomethyl-tetracycline or its acetate.

16. Piperidinomethyl-oxytetracycline or its acetate.

17. A process for the manufacture of new, water-soluble, physiologically tolerable aminomethylation products of the tetracyclines as defined in claim 1, wherein an anti-bacterial isomeric form of tetracycline, chloro-tetracycline or hydroxytetracycline corresponding to the general formula



in which R_3 and R_4 have the meanings given in claim 1, or an anti-bacterial isomeric form of anhydro-tetracycline, is aminomethylated (Mannich reaction) so as to introduce the aminomethyl radical

$$-CH_2-N<^{R_1}_{R_2}$$

in which R_1 and R_2 have the meanings given in claim 1.

18. A process as claimed in claim 17, wherein the free tetracycline, chloro-tetracycline, hydroxy-tetracycline or anhydro-tetracycline is used as starting material.

19. A process as claimed in claim 17, wherein a salt of the tetracycline, chloro-tetracycline, hydroxy-tetracycline or anhydro-tetracycline with an inorganic or organic acid or with an inorganic or organic base is used as starting material.

20. A process as claimed in claim 17, 18 or 19, wherein formaldehyde and ammonia or an amine are used for the aminomethylation.

21. A process as claimed in claim 20, wherein the formaldehyde is used in the form of a substance yielding formaldehyde under the conditions of the reaction.

22. A process as claimed in claim 20 or 21, wherein a primary or secondary aliphatic amine is used.

23. A process as claimed in claim 20 or 21, wherein a heterocyclic amine is used.

24. A process as claimed in claim 17, 18 or 19, wherein the tetracycline, chloro-tetracycline, hydroxy-tetracycline or anhydro-tetra-

cycline is reacted with an aminomethyl-compound capable of bringing about trans-aminomethylation (as hereinbefore defined).

25. A process for the manufacture of a water-soluble aminomethylation product of a tetracycline, conducted substantially as described in any one of the Examples herein.

26. Physiologically tolerable aminomethylation products of the tetracyclines, whenever made by the process claimed in any one of claims 17—25.

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