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(54) 2,4,7-TRIAMINO-6-(P-SUBSTITUTED PHENYL)-PTERIDINES, THEIR PREPARATION AND PHAMACEUTICAL COMPOSITIONS THEREOF

(71) We, RÖHM PHARMA, G.m.b.H., a German Body Corporate, of Darmstadt, 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 invention relates to 2,4,7-triamino-6-(*p*-substituted phenyl)-pteridines having diuretic and anti-hypertensive properties which are useful in heart and coronary therapy, and to pharmaceutical compositions thereof.

A well-known use of diuretically active substances is the treatment of oedema. Relatively good therepeutic results have been achieved for example, with saluretics (used herein in the strict sense to denote a substance which displays salt-separating activity directly by inhibition of sodium reverse resorption in the renal tubes and secretes mainly chloride ions as the anion).

With the discovery of the hypotensive properties of saluretics, their area of use has been considerably enlarged. In particular, in the treatment of essential hypertension which is not accessible to causal treatment and accounts for approximately 80% of all hypertensive cases, saluretics have a particularly important role. Important representatives of this group of compounds are benzothiadiazine derivatives such as chlorothiazide and hydrochlorothiazide. However, depending on the electrolytic regime of the patient, the use of benzothiadiazine derivatives is subject to serious limitations. In patients with existing liver and kidney diseases, therapy with this group of compounds may present serious risks. Also, in prolonged treatment, dangerous disturbances of the electrolytic and fluid regime can occur (e.g. hypochloroaemia, hypocalcaemia, hypokalaemia and alkalosis). Especially undesirable is the loss of potassium ions when using saluretics alone.

The development of "potassium-retaining" diuretics has, therefore, been undertaken. One aim was the competitive inhibition of the adrenal cortical hormone aldosterone which (in normal metabolism) promotes sodium reverse resorption and potassium secretion in the renal tubes. The aims has been achieved to some extent with the steroid derivative spironolactone, although therapy generally requires high dosages (0.2 to 1 g per day). Potassium-retaining diuretics which do not act via competitive inhibition of aldosterone include amiloride (N-amidino-3 ,5-diamino-6-chloropyrazine carboxamide) and triamterene (2,4,7-triamino-6-phenylpteridine).

Triamterene has provded to be an extremely valuable active therepeutic substance either alone or in combination e.g. with saluretics in oedema and high blood pressure therapy. As a result, studies have been made of the active mechanism and metabolism of triamterene. Model tests on the main excretory duct of the salivary gland of rats (whose epithelium is similar in function to the distal renal tube) have resulted in triamterene completely blocking sodium ion reverse resorption and reducing potassium ion secretion by half. The model tests on the excretory duct of the salivary gland is fully in accordance with findings in the kidney and can be considered as a reliable indication of the "potassium-retaining" diuretic activity of triamterene [H, Knauf *et al* Europ. J.Clin. Invest. *6*, 43 (1976)]. Furthermore,

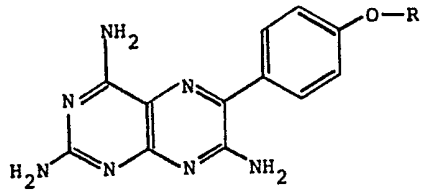
triamterene has a cardio-protective effect. An anti-arrythmic effect for triamterene can be proved by electro-physiological measurements on the individual myocardial fibres of isolated papillary muscles of guinea pigs [B. Luderitz et al. Verh.Dtsch.Ges.Kreislaufforschung *41*, 305 (1975)].

Although triamterene fulfils very well the therepeutic requirements of a diuretic, including a low level of side effects the search has continued for even better therapeutic materials. A distinct disadvantage of triamterene is its low solubility in water which renders parenteral application difficult. Thus, starting from the pteridine structure, studies have been carried out with a systematic variation of substituents to investigate the connection between structure and (diuretic) activity [L. Weinstock et al. J. Med. Chem. *11*, 573-579 (1968)].

The triamterene derivatives which showed noteworthy diuretic activity were generally those compounds which possess non-polar substituents such as the p-toluyl homologues of triamterene. Derivatives with polar groups, e.g. amino or nitro groups, were diuretically inactive according to the findings of Weinstock (*loc. cit.* Table VIII).

It is an object of the present invention to provide new and advantageous pteridine compounds and pharmaceutical compositions thereof possessing valuable diuretic properties.

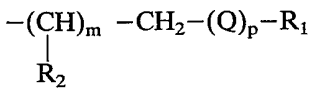
According to one aspect of the invention we provide pteridine compounds of formula I



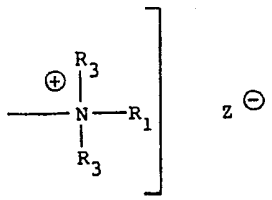
(I)

wherein R represents a hydrophilic group selected from

(a) a radical of formula



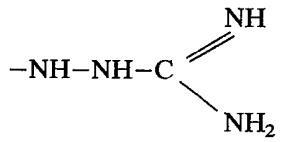
(in which p is an integer having a value of 0 or 1; R_1 represents a hydrogen atom or a methyl or ethyl group; R_2 represents a hydroxy group, a hydrogen atom or an alkyl group containing 1-4 carbon atoms; and Q represents an oxygen or sulphur atom or a radical of formula $-NR_3$ [wherein R_3 represents a hydrogen atom or a methyl or ethyl group]; or $-(Q)_p-R_1$, when p is 1, together represent a substituted ammonium ion of formula



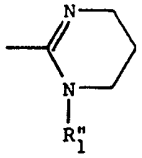
[wherein R_1 and R_3 are as defined above and $Z^{\ominus}$ represents a physiologically acceptable anion]; and m is an integer having the values 0, 1, 2 or 3 subject to the following provisos:
1) that when m is 2 or 3, then the groups represented by R_2 in the hydrocarbon chain represented by $-(CH_2)_m-$ may be the same or different; and
2) that when p is 0, then m is 1, 2 or 3 and at least one of the groups represented by R_2 is a hydroxyl group);

(b) a radial of formula $-(CH_2)_nCY$ (wherein n is an integer having the value 0, 1, 2, 3 or 4; and Y represents a hydroxy group or a physiologically acceptable salt thereof, a group of formula $-NR_4R_5$ (in which R_4 and R_5, which may be the same or different, each represents a hydrogen atom or a straight-chain or branched alkyl group containing 1-4 carbon atoms), a group of formula $-(O)_r-R_6$ (wherein R_6 represents an alkyl group containing 1-6 carbon atoms and r is an integer having the value of 0 or 1), or a group of formula $-(CH_2)_q-R_7$ (in which q is an integer having the value of 0, 1 or 2, and R_7 represents a morpholinyl,

pyrrolidinyl, piperidinyl or piperazinyl radical which can be bonded via a carbon atom or [provided q is other than 0] via a nitrogen atom, or a substituted ammonium derivative of the said morpholinyl, pyrrolidinyl, piperidinyl or piperazinyl radical with a compound of formula R'_1Z' [in which R'_1 and Z' respectively have the same meanings as R_1 and Z, above], a radical of formula

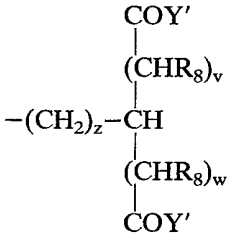


or a radical of formula

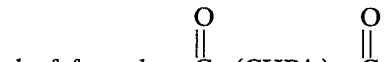


[in which R'_1' has the same meaning as R_1 above]);

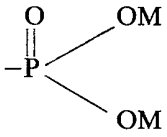
(c) a radical of formula



(in which Y' has the same meaning as Y above; each R_8 may be the same or different and represents a hydrogen atoms or a hydroxy group; and v, w and z, which may be the same or different, each is an integer having a value of 0, 1 or 2);

(d) a radical of formula 
(in which s is an integer having a value of 0, 1, 2, 3 or 4, and R'_8 and Y'' respectively have the same meanings as R_8 and Y above);

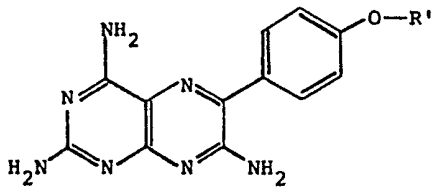
(e) a radical of formula



(in which M represents a hydrogen atom or a physiologically acceptable cation); and

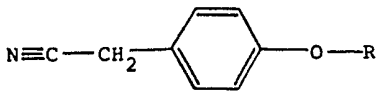
(f) a group of formula $-CH_2-OAr$ (in which Ar represents a phenyl radical if desired substituted by chlorine) or an alkyl radical containing 1-3 carbon atoms substituted by one or more chlorine atoms.

The compounds of formula I possess useful therapeutic properties. Especially preferred are compounds of formula I which provide an improved solubility in water in comparison with the compound triamterene and with the compounds of formula IB wherein R^1 represents hydrogen atom or a methyl group.



(IB)

According to a further aspect of the present invention we provide a process for the preparation of compounds of formula I (as defined above) which comprises
(a) reacting 2,4,6-triamino-5-nitroso-pyrimidine with a compound of formula III



(III)

(in which R is as defined above); or, as a less generally applicable process,
b) reacting a compound of formula IV

XR (IV)

(wherein R is as defined above; and X represents a radical which may act as a leading group in acylation/alkylation reactions, preferably a chlorine or bromine atom or, if R represents a group of formula

(wherein Y is as defined above) 0, a group of formula [in which R_4' is as defined for Y]) with a compound formula IB (wherein R′ is represents an alkali metal cation, such as, for example, sodium or potassium) or with a compound of formula IB (in which R′ represents a hydrogen atom), in the presence of an acid acceptor.

The preparation of the compounds of formula IB can be carried out in conventional manner.

The choice of the process and reaction conditions to be used in preparing the compounds of formula I will depend *inter alia* on such factors as the relative accessibility of the appropriate starting materials and the probability of forming by-products, e.g. by reaction of the amino functions, and the ease with which separation and purification can be carried out. It should be noted, for example, that the substituents R are generally sufficiently stable under the conditions usually employed according to process a).

The preparation of the compounds of formula I can be carried out as follows according to process a): 2,4,6-triamino-5-nitroso-pyrimidine is reacted, if desired in suspension, with the compound of formula III in an inert reaction medium, e.g. dimethylformamide of N,N-dimethyl acetamide, preferably in the presence of an alkali metal hydroxide or amide or an alkali metal alcoholate of a C_1 to C_4 alcohol, for example, in an alkoxyalkanol such as 2-ethoxyethanol, or methanol, at elevated temperature.

The reaction time is, as a rule, kept as short as possible, for example, when work is carried out at reflux temperature. The mixture can be worked up in the conventional manner.

Decomposition of the reagents and/or the final product can be prevented, for example, by working at the lowest possible reaction temperature, and by the use of alkali metal alcoholates with low nucleophilicity, such as potassium tert-butoxide.

The preparation of compounds of formula I according to process b) can be carried out as follows:
a compound of formula IB (in which R′ is an alkali metal cation) in an inert solvent e.g. a nitrile such as acetonitrile, an amide such as N,N-dimethylformamide or hexamethyl phosphoric acid triamide, an alcohol such as tertiary butanol or an amine such as pyridine or N,N-dimethylaniline, or in a mixture of solvents, or in suspension, preferably with stirring, between room temperature and 120°C or the boiling point of the solvent, is treated with a compound of formula IV, if desired in a suitable solvent, for example one of the

aforementioned solvents, optionally in the presence of an acid acceptor e.g. tertiary amine such as triethylene, N,N-dimethylaniline or N-methyl-morpholine.

To complete the reaction, the mixture is stirred for a certain period, for example 2-24 hours, after which time the mixture can be worked up in the conventional manner.

When R' in the compound of formula IB represents a hydrogen atom and the compound of formula IV contains a carboxy group, the reaction (with elimination of water) is preferably carried out in the presence of a condensation agent, advantageously dicyclohexylcarbodiimide. The reaction can be effected for example in an inert solvent medium, such as, for example, acetone or pyridine, preferably with warming, and conveniently over a long period, for example 1-14 days.

The compounds of formula I are, as a rule, crystalline, relatively high-melting compounds (partly with decomposition). They can be re-crystallised, for example, from aqueous solutions, if desired with the addition of formamide or acetonitrile, or from acids, such as formic, acetic or phosphoric acid.

The compounds of general formula I are valuable therapeutic compounds having a pronounced diuretic activity with simultaneous potassium retention, as well as extra-renal, especially cardio-protective activities.

We have found that the compounds of formula I have advantageous properties, for example over the triamterene, and thus represent an advance in the art. For a direct comparison of diuretic and potassium-retaining activity, tests on the epithelium of the main excretory duct of the submaxiliary gland of rats according to Knauf (*loc.cit.*) can be used. As an indication of the cardio-protective effect the electro-physiological tests on isolated heart structures of guinea pigs and dogs according to Luderitz (*loc.cit*) can be employed.

The compounds of formula I also tend to have a better solubility in water than triamterene. Particularly improved solubility in water is generally to be expected in the compounds of formula I which have groups with pronounced salt-forming (strongly basic or acid) properties.

In this respect, those compounds of general formula I in which an amine or an ammonium group stands in a position β- to the phenolic oxygen are especially preferred.

The compounds of formula I (as defined above) may be formulated for parenteral administration as well as for oral administration, especially when they are present in salt form.

According to a yet further aspect of the present invention we therefore provide pharmaceutical compositions, advantageously adapted for oral or parenteral administration, comprising as active ingredient at least one compound of formula I (as defined above) together with at least one pharmaceutical carrier and/or excipient.

The compounds of formula I can be administered in doses depending on the type of indication and the individual requirement of the patient.

Because of the improved diuretic activity over triamterene, the dosage of the compound of formula I used in practice will generally be below that of triamterene; thus, in many cases, the normal dosages of triamterene can therefore be considered as an upper limit of the dosage range of the active substances of formula I.

The pharmaceutical compositions according to the invention can be formulated in conventional manner e.g. with conventional carriers and adjuvants. A particularly preferred embodiment of the invention is represented by solid compositions intended for oral administration, such as, for example, tablets (as well as coated tablets) and capsules. Pharmaceutically inert solids such as, for example, mannitol, lactose and organic or inorganic calcium salts can be used as carrier materials for oral application. Polyvinyl pyrrolidone, gelatin or cellulose derivatives are suitable examples of binding agents. As further additives, tablet disintegrating agents such as starch of alginic acid, lubricating agents such as stearic acid or its salts and inorganic lubricants such as talc or colloidal silicic acid, as well as other pharmacologically inactive agents such as, for example, flavour correcting agents can be used.

The active ingredients can be conventionally mixed with the adjuvants and granulated wet or dry. Depending on the type of additives used, a powder which can be made directly into tablets can be obtained optionally also by simple mixing. The granules or powder can be filled directly into capsules or pressed conventionally into tablet cores.

For parenteral administration the therapeutic agents can likewise be prepared and administered conventionally.

The following Examples illustrate the present invention.

EXAMPLE 1

2,4,7-triamino-6-(p-acetoxy-phenyl)-pteridine

410 mg of metallic sodium are dissolved with stirring in 100 ml of 2-ethoxyethanol. 1100 mg of 2,4,6-triamino-nitrosopyrimidine and 1140 mg of p-acetoxybenzyl-cyanide are added

in succession with stirring and heated to boiling with stirring. The colour of the mixture changes from violet to brown. After refluxing for 2 hours the heating is switched off and the reaction mixture is allowed to cool. 70 to 80% of the 2-ethoxyethanol are subsequently drawn off in a water-pump vacuum and the residue is taken up in 500 ml of water. After extracting four times with diethyl-ether, the mixture is adjusted to a pH value of 5 with 2N hydrochloric acid. The precipitate is filtered off, washed with ice-cold acetone and recrystallised from 10% acetic acid. Further purification can be carried out through a silica gel column. The title compound is obtained which decomposes at 319-321°C (carbonisation).

The reaction can also be carried out advantageously with the use of an alkali metal alcoholate in methanol.

EXAMPLE 2

2,4,7-triamino-6-(p-2-hydroxyethoxyphenyl)-pteridine

460 mg of metallic sodium are dissolved with stirring in 150 ml of 2-ethoxyethanol. 3.1 g (0.02 mol) of triamino-nitrosopyridimide and 3.5 g (0.02 mol) of *p*-(2-hydroxy-ethoxy)-phenylacetonitrile are successively added with stirring and heated in a water bath to 60°C with stirring. The colour of the mixture changes from violet to light brown. After stirring for 14 hours the reaction is completed. The mixture is allowed to cool. Unreacted 2,4,6-triamino-nitrosopyrimidine is filtered off and the clear solution is evaporated to dryness. The deposit is taken up in hot acetone and the crude product is precipitated by mixing with petroleum ether. Purification is carried out once by recrystallisation from butanol and then by separation on a silica gel drying column (silica gel 60 Merck [Merck is a registered Trade Mark]). The title compound is obtained as yellow-brown crystals. Decomposition starting at 250°C. Rf value = 0.55 uniform with chloroform/methanol (70:30) eluent on silica gel thin-layer plates.
Elementary analysis: $C_{14}H_{15}N_7O_2$ (313.3).

EXAMPLE 3

2,4,7-triamino-6-(p-2,3-dihydroxypropoxy-phenyl)-pteridine

Analogously to Example 2, 2,4,7-triamino-6-(*p*-2,3-dihydroxypropoxy-phenyl)-pteridine can also be prepared. Rf value = 0.50 uniform with chloroform/methanol (70:30) eluent on silica gel thin-layer plates.
Elementary analysis: $C_{15}H_{17}N_7O_3$ (341.3).

EXAMPLE 4

2,4,7-triamino-6-(p-succinoyloxyphenyl)-pteridine

0.63 g (0.0055 mol) of succinic acid, 1.35 g (0.005 mol) of *p*-hydroxytriamterene and 1.12g (0.05 mol) of dicyclohexylcarbodiimide are added to dry acetone and the mixture is heated to boiling for 14 days with the exclusion of water. The reaction is terminated and the solvent is removed. The residue obtained is washed several times with diethyl-ether. The remaining residue is absorbed in as little DMF as possible (5 to 10 ml) and diluted with four times the volume of acetone. The solution is applied to a Sephadex-LH 20 column suspended in acetone (Sephadex is a registered Trade Mark). The final product is obtained after eluting off a preliminary fraction. It is obtained by concentrating the acetone solution. Rf value = 0.30 with chloroform/methanol (70:30) eluent on silica gel thin-layer plates.

EXAMPLE 5

2,4,7-triaminio-6-(p-adipoyloxyphenyl)pteridine

2,4,7-Triamino-6-(*p*-adipoyloxyphenyl)-pteridine can also be prepared in an analogous manner to the compound of Example 4.
Rf value = 0.31 with chloroform/methanol (70:30) eluent on a silica gel thin-layer plate.

The starting compounds of formula III can be prepared, for example as follows:

Preparation of p-(2-hydroxyethoxy)-phenylacetonitrile

5 g of *p*-hydroxyphenylacetonitrile are dissolved in 250 ml of methylethylketone. 7 g of 2-bromoethanol and 23g of potassium carbonate are added thereto. The mixture is refluxed with stirring for 48 hours. After completion of the reaction, potassium carbonate and the potassium bromide obtained are filtered off. The deposits are washed with acetone and the washing acetone is combined with the reaction mixture. The clear solution is concentrated to approximately 10 to 15 ml. It is taken up in diethyl-ether and shaken with 1/100N sodium hydroxide solution. The ether phase is dried over sodium carbonate and the ether is then distilled off. The title compound is obtained as a yellowy oil.
Rf = value 0.70 with acetone/carbon tetrachloride (1:1) eluent on silica gel thin-layer plates.

Preparation of p- (2,3-dihydroxypropoxy)-phenylacetonitrile

Analogously to *p*-(2-hydroxyethoxy)-phenylacetonitrile, *p*-(2,3-dihydroxpropoxy)-phenylacetonitrile can also be prepared, shaking with water being carried out instead of with sodium hydroxide solution. The product is in the aqueous phase and, when concentrated, a colourless, crystalline deposit is precipitated. Rf value = 0.60 with acetone/carbon tetrachloride (1:1) eluent on silica gel thin-layer plates.

The following Examples illustrate the preparation of pharmaceutical compositions according to the invention:

a) *Preparation of tablets resistant to gastric juices*

The tablet cores are prepared from the following composition:
15 mg 2,4,7-triamino-6-(*p*-acetoxyphenyl)-pteridine
as pharmaceutically active ingredient
10 mg of magnesium stearate
12 mg of talc
8 mg of Aerosil (Aerosil is a registered Trade Mark)
95 mg of lactose, granulate
55 mg of lactose, finely crystalline
25 mg of corn starch
80 mg of cellulose, granulate

The ingredients are mixed in an intensive mixer (Lödige type) and pressed into tablets weighing 300 mg each. Tablets are obtained with a breaking strength of 6.5 to 8.5 (determined on a ERWEKA breaking strength tester; decomposition in water at 37°C: 2.5 minutes).

To prepare the coating resistant to gastric juices a lacquer suspension is applied to the tablet cores. On 4 kg of the cores preheated to 40°C a lacquer suspension is applied, containing
100 g of polyacrylic resin lacquer dispersion with a
30% dry solids content;
300 g of a pigment suspension containing
120 g of solids; and
600 g of water.
The polyacrylic resin lacquer contains a copolymer of ethyl acrylate and methacrylic acid (1:1).

The pigment suspension has the following composition:
50 g of talc
63 g of titanium dioxide
42 g of coloured lacquer
90 g of polyethylene wax 600°, 33% in water
30 g of emulsifier (Tween 80), 33% in water
200 g of Tylose C 30, 3% in water (water-soluble cellulose ether)
15 g of cellulose, finely crystalline
183 g of lactose
1 g of anti-foam emulsion
326 g of water
(Tween and Tylose are registered Trade Marks)
After a spraying time of approximately 40 minutes, tablets with a resistance to gastric juices of at least 3 hours are obtained

Analogously to the description for 2,4,7-triamino-6-(*p*-acetoxyphenyl)-pteridine, other compounds of formula I can be formulated, for example
2,4,7-triamino-6-(*p*-2-hydroxyethoxyphenyl)-pteridine
2,4,7-triamino-6-(2,3-dihydroxy-propoxy-phenyl)-pteridine
2,4,7-triamino-6-(*p*-succinoyloxyphenyl)-pteridine
2,4,7-triamino-6-(*p*-adipoyloxy-phenyl)-pteridine

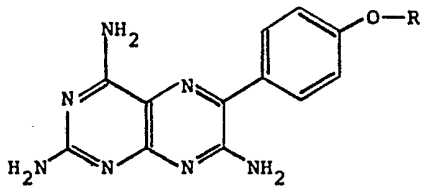
b) *Preparation of a pharmaceutical composition suitable for parenteral, particularly intravenous, administration*

25 mg of 2,4,7-triamino-6-(*p*-hydroxyphenyl)-pteridine are treated at room temperature with 10 ml of a 10% aqueous solution of dimethylaminoethanol. The pharmacologically active substance is dissolved. The mixture is then diluted to 100 ml with physiological saline. A clear, yellowy solution is obtained with a pH value of 10.9.

Analogously to the description for 2,4,7-triamino-6-(*p*-hydroxyphenyl)-pteridine, compounds of formula I can also be formulated, for example
2,4,7-triamino-6-(*p*-acetoxyphenyl)-pteridine
2,4,7-triamino-6-(*p*-2-hydroxyethoxyphenyl)-pteridine
2,4,7-triamino-6-(2,3-dihydroxy-propoxy-phenyl)-pteridine
2,4,7-triamino-6-(p-succinoyloxyphenyl)-pteridine
2,4,7-triamino-6-(p-adipoyloxyphenyl)-pteridine.

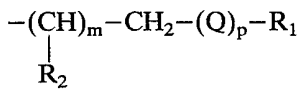
WHAT WE CLAIM IS:-

1. Pteridine compounds of general formula I

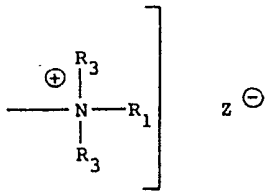


(I)

wherein R represents a hydrophilic group selected from
(a) a radical of formula

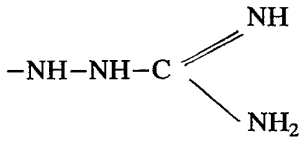


(in which p is an integer having a value of 0 or 1; R_1 represents a hydrogen atom or a methyl or ethyl group; R_2 represents a hydroxy group, a hydrogen atom or an alkyl group containing 1-4 carbon atoms; and Q represents an oxygen or sulphur atom or a radical of formula $-NR_3-$[wherein R_3 represents a hydrogen atom or a methyl or ethyl group]; or $\overline{(Q)_p}-R_1$, when p is 1, together represent a substituted ammonium ion of formula

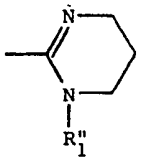


[wherein R_1 and R_3 are as hereinbefore defined and $Z^{\ominus}$ represents a physiologically acceptable anion]; and m is an integer having the values 0, 1, 2 or 3
subject to the following provisos:
1) that when m is 2 or 3, then the groups represented by R_2 in the hydrocarbon chain represented by $-(CH_2)_m-$ may the same or different; and
2) that when p is 0, then m is 1, 2 or 3 and at least one of the groups represented by R_2 is a hydroxyl group);

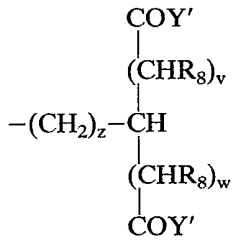
(b) a radical of formula $-(CH_2)_n\overset{O}{\overset{\|}{C}}Y$ (wherein n is an integer having the value 0, 1, 2, 3 or 4; and Y represents a hydroxy group or a physiologically acceptable salt thereof, a group of formula $-NR_4R_5$ (in which R_4 and R_5, which may be the same or different, each represents a hydrogen atom or a straight-chain or branched alkyl group containing 1-4 carbon atoms), a group of formula $-(O)_r-R_6$ (wherein R_6 represents an alkyl group containing 1-6 carbon atoms and r is an integer having the value of 0 or 1), or a group of formula $-(CH_2)_q-R_7$ (in which q is an integer having value of 0, 1 or 2, and R_7 represents a morpholinyl, pyrrolidinyl, piperidinyl or piperazinyl radical which can be bonded via a carbon atom or [provided q is other than 0] via a nitrogen atom, or a substituted ammonium derivative of said morpholinyl, pyrrolidinyl, piperidinyl or piperazinyl radical with a compound of formula R'_1Z' [in which R'_1 and Z' respectively have the same meanings as R_1 and Z, above], a radical of formula



or a radical of formula

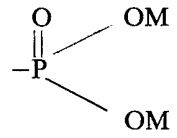


[in which R''_1 has the same meaning as R_1 above]);
(c) a radical of formula



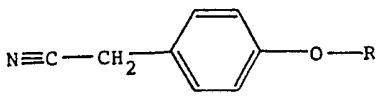
(in which Y' has the same meaning as Y above; each R_8 may be the same or different and represents a hydrogen atom or a hydroxy group; and v, w and z, which may be the same or different, each is an integer having a value of 0, 1 or 2);

(d) a radical of formula 
(in which s is an integer having a value of 0, 1, 2, 3 or 4, and R'_8 and Y'' respectively have the same meanings as R_8 and Y above);
(e) a radical of formula



(in which M represents a hydrogen atom or a physiologically acceptable cation); and
(f) a group of formula $-CH_2-OAr$ (in which Ar represents a phenyl radical if desired substituted by chlorine) or an alkyl radical containing 1-3 carbon atoms substituted by one or more chlorine atoms.

2. 2,4,7-Triamino-6-(*p*-acetoxyphenyl)-pteridine
3. 2,4,7-Triamino-6-[*p*-(2-hydroxyethoxy)-phenyl]-pteridine.
4. 2,4,7-Triamino-6-[p-(2,3-dihydroxypropoxy)-phenyl]-pteridine.
5. 2,4,7-Triamino-6-[p-succinoyloxyphenyl]-pteridine.
6. 2,4,7-Triamino-6-[p-adipoyloxyphenyl]-pteridine.
7. Compounds of formula I (as defined in claim 1) as herein specifically described with the exclusion of compounds of formula I as claimed in claims 2 to 6.
8. A process for the preparation of compounds of formula I (as defined in claim 1) which comprises
a) reacting 2,4,6-triamino-5-nitroso-pyrimidine with a compound of formula III



(III)

(in which R is as defined in claim 1); or
b) reacting a compound of formula IV

$$X-R \qquad (IV)$$

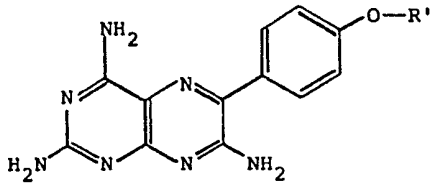
(wherein R is as defined in claim 1 and X represents a radical which may act as a leaving group in an acylation/alkylation reaction or, if R represents a group of formula

$$-\overset{\overset{O}{\|}}{C}Y$$

(wherein Y is as defined in claim 1), a group of formula

$$-O-\overset{\overset{O}{\|}}{C}-R'_4$$

[in which R'_4 is as defined for Y]) with a compound of formula IB



(IB)

(wherein R′ represents an alkali metal cation) or with a compound of formula IB (wherein R′ represents a hydrogen atom), in the presence of an acid acceptor.

9. A process as claimed in claim 8 wherein a compound of formula IV is used in which X represents a chlorine or bromine atom.

10. A process as claimed in claim 8 wherein reaction
a) is effected in the presence of an alkali metal hydroxide or amide, or alkali metal alcoholate of a C_1 to C_4 alcohol.

11. A process as claimed in claim 8 or claim 9 wherein the said acid acceptor in reaction b) comprises a tertiary amine.

12. A process as claimed in claim 8 substantially as herein described.

13. A process for the preparation of compounds of formula I (as defined in claim 1) substantially as herein described in any of Examples 1 to 5.

14. Compounds of formula I (as defined in claim 1) whenever prepared by a process as claimed in any of claims 8 to 13.

15. Pharmaceutical compositions comprising as active ingredient at least one pteridine compound of formula I (as defined in claim 1) together with at least one pharmaceutical carrier and/or excipient.

16. Compositions as claimed in claim 15 wherein the active ingredient comprises 2,4,7-triamino-6-(*p*-acetoxy-phenyl)-pteridine.

17. Compositions as claimed in either of claims 15 and 16 adapted for oral administration.

18. Compositions as claimed in either of claims 15 and 16 adapted for parenteral administration.

19. Compositions as claimed in any one of claims 15 to 18 substantially as herein described.

20. Pharmaceutical compositions as claimed in claim 15 substantially as herein described in either of Examples a) and b).

For the Applicant,
FRANK B. DEHN & CO.,
Chartered Patent Agents,
Imperial House,
15 - 19 Kingsway,
London, W.C.2.

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