United States Patent Office

3,560,504

Patented Feb. 2, 1971

3,560,504

VIROSTATICALLY EFFECTIVE SUBSTITUTED 3-ALKENYL-5-ETHYL URACIL COMPOUNDS

Kailash Kumar Gauri, Lentfohrden, Holstein, Germany, assignor to Robugen G.m.b.H., Esslingen am Neckar, Germany, a company of Germany

No Drawing. Filed Sept. 3, 1968, Ser. No. 757,146
Int. Cl. C07d *51/30*
U.S. Cl. 260—260 12 Claims

ABSTRACT OF THE DISCLOSURE

Highly effective virostatic agents are substituted 5-ethyl uracil compounds which have alkenyl with 3 to 6 carbon atoms in 3-position and may be substituted in 1-position by alkyl with 1 to 4 carbon atoms, cycloalkyl, aryl, or aralkyl and in 4-position by halogen. Examples of such compounds are 1,5-diethyl-3-allyl-4-chloro uracil, 1-methyl-3-allyl or crotyl-4-chloro-5-ethyl uracils, 1-methyl or ethyl-3-allyl or crotyl-5-ethyl uracils. They are preferably obtained by alkenylation in 3-position of the corresponding 5-ethyl uracil compounds which have in 3-position hydrogen. They are preferably topically applied to the virus-affected areas of the body in the form of solutions, ointments, powders, sprays, or the like which contain between about 0.5% and about 50% thereof.

BACKGROUND OF THE INVENTION

(1) Field of the invention

The present invention relates to new and valuable uracil compounds and more particularly to virostatically effective 5-ethyl uracil compounds, to a process of their manufacture, to pharmaceutical compositions containing same, and to a method of using same in the therapy of virus infections.

(2) Description of the prior art

5-alkyl substituted uracil compounds are known (M. Muraoka, A. Takada, and T. Ueda "Keio J. Med.," vol. 11 (1962) page 95; see "Chem. Abstracts," vol. 57 (1962), page 17192*b*). These compounds were found to be virostatically ineffective. 1,5-disubstituted uracil compounds have also no virostatic activity.

SUMMARY OF THE INVENTION

It is one object of the present invention to provide highly virostatically effective compounds of the uracil group which are characterized by being substituted in 3-position or, respectively, in 3-, and 4-position and may be substituted in 1-position and which have ethyl in 5-position.

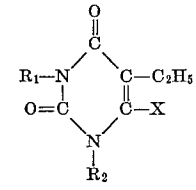
Another object of the present invention is to provide a simple and effective process of producing such substituted 5-ethyl uracil compounds.

A further object of the present invention is to provide virostatically effective compositions containing such substituted 5-ethyl uracil compounds as active ingredients.

Still another object of the present invention is to provide a method of treating patients affected by virus infections with such disubstituted 5-ethyl uracil compounds.

Other objects of the present invention and advantageous features thereof will become apparent as the description proceeds.

In principle the virostatically effective 5-ethyl uracil compounds according to the present invention are compounds of the following Formula I:



(I)

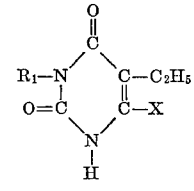
In said formula

R_1 indicates straight chain or branched alkyl with 1 to 4 carbon atoms, preferably methyl or ethyl, cycloalkyl, aryl, or aralkyl, which alkyl, aryl, or aralkyl may be substituted;

R_2 indicates straight chain or branched alkenyl with 3 to 6 carbon atoms, preferably allyl or crotyl; and

X indicates hydrogen or halogen, preferably chlorine.

A preferred process of producing such compounds comprises reacting 5-ethyl uracil compounds of Formula II



(II)

wherein R_1 and X represent the same substituents as indicated above, with an alkenyl halogenide, such as allylbromide, in the presence of a basic agent capable of binding acids, for instance, potassium carbonate, in a suitable solvent or solvent mixture or even without solvent whereby the alkenyl halogenide serves as solvent.

The starting materials, i.e., the compounds of Formula II are produced, for instance, as described in German Pats. Nos. 1,215,718 or 1,250,829.

It is highly surprising that these substituted 5-ethyl uracil compounds in contrast to the known 5-alkyl substituted uracil compounds and also to 1,5-disubstituted uracil compounds have a high virostatic activity. The compounds are not only effective against DNA-vira, for instance, against *Herpes simplex* but also against RNA-vira, for instance, against foot-and-mouth-disease. Their activity is therefore far superior to that of other known virostatic agents such as iodo deoxyuridine or p-fluoro phenyl alanine. In addition thereto they are of surprisingly low toxicity.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples serve to illustrate the present invention without, however, limiting the same thereto.

Example 1

20.3 g. of 1,5-diethyl-4-chloro uracil are heated under reflux with 36.3 g. of allylbromide and 16.6 g. of freshly calcined potassium carbonate in 120 cc. of dried acetone and 80 cc. of dried dimethylformamide for 24 hours. Care is taken that moisture is excluded during the reaction. After cooling, the reaction mixture is filtered to remove solid matter. The mixture of solvents and excess allylbromide is distilled off in a vacuum and the residue is subjected to fractional distillation in a vacuum. The resulting 1,5-diethyl-3-allyl-4-chloro uracil has a boiling point of 115–120° C./0.1 mm. Hg, refractive index

$$n_{23.5°}^{D}=1.5297$$

The yield is 21.8 g. corresponding to 90% of the theoretical yield.

Analysis.—Calculated for $C_{11}H_{15}ClN_2O_2$ (percent): C, 54.44; H, 6.23; N, 11.54. Found (percent): C, 54.38; H, 6.29; N, 11.46. Molecular weight: 242.70.

In an analogous manner there are produced the following compounds of Formula I:

TABLE I

Example No.	R_1	R_2	X	Boiling point °C.	Boiling point mm. Hg	Empirical formula	Molecular weight	Analysis, percent Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
2	CH_3	CH_2—CH=CH_2	Cl	140–141	0.3	$C_{10}H_{13}ClN_2O_2$	228.69	52.52	5.73	12.25	52.57	5.69	12.22
3	CH_3	CH_2—CH=CH—CH_3	Cl	145–147	0.4	$C_{11}H_{15}ClN_2O_2$	242.70	54.44	6.23	11.54	54.42	6.30	11.54
4	C_2H_5	CH_2—CH=CH_2	H	138	0.3	$C_{11}H_{15}N_2O_2$	208.26	63.43	7.74	13.45	63.38	7.78	13.49
5	C_2H_5	CH_2—CH=CH—CH_3	H	150–152	0.2	$C_{12}H_{18}N_2O_2$	222.29	64.84	8.16	12.60	64.78	8.24	12.59

In place of the starting uracil compounds used in the preceding examples, there may be employed equimolecular amounts, for instance, of isopropyl-4-chloro-5-ethyl uracil, 1-n-butyl-4-bromo-5-ethyl uracil, 1-phenyl-4-iodo-5-ethyl uracil, 1-p-tolyl-4-chloro-5-ethyl uracil, 1-benzyl-4-chloro-5-ethyl uracil, 4-chloro-5-ethyl uracil, 1-cyclohexyl-4-chloro-5-ethyl uracil, and the like compounds while otherwise the procedure is the same as described hereinabove.

In place of the alkenyl halogenides used as the other reaction component in the preceding examples, there may be employed equimolecular amounts, for instance, of 1-chloro-2-pentene, 1-bromo-2-hexene, 1-chloro-3-methyl-2-butene, 1-bromo-2,3-dimethyl-2-butene, 1-chloro-3-butene, and the like compounds while otherwise the procedure is the same as indicated above.

As stated hereinabove, the new substituted 5-ethyl uracil compounds are topically applied to the virus-infected areas of the body in the form of solutions, emulsions, creams, ointments, powders, sprays, and the like preparations. The amount of the active agent in such pharmaceutical preparations may vary. Amounts between 0.5% and 50% and even more may be admixed to the pharmaceutical excipients, ointment bases, solvents, and the like. Preferred amounts of the virostatically active agent in such preparations are amounts between about 1.0% and 10.0%.

The following examples serve to illustrate the preparation of suitable pharmaceutical preparations according to the present invention without, however, being limited thereto.

Example 6

10.0 g. of 1,5-diethyl-3-allyl-4-chloro uracil are dissolved in 10.0 g. of propylene glycol and 80 g. of 50% ethanol. The resulting solution is repeatedly applied to the virus affected area of the skin or to the lips.

Example 7

50.0 g. of 1,5-diethyl-3-allyl-4-chloro uracil are dissolved in 50.0 g. of dimethylsulfoxide. The resulting solution is repeatedly applied to the virus-affected areas of the body.

Example 8

1.0 g. of 1,5-diethyl-3-allyl-4-chloro uracil is dissolved in 3.0 g. of the polyoxy ethylene ester of castor oil sold under the trademark ORPE by Fabenfabriken Bayer of Opladen, Germany, and 96 g. of physiological (0.9%) sodium chloride solution is added. The resulting mixture is applied to the virus affected parts of the body.

Example 9

0.5 g. of 1-methyl-3-allyl-4-chloro-5-ethyl uracil is dissolved in 99.5 g. of the liquid saturated fatty alcohol mixture consisting mainly of 2-octyl dodecanol and sold under the trademark "Eutanol G" by Deutsche Hydrierwerke G.m.b.H. of Duesseldorf, Germany.

Example 10

10.0 g. of 1-methyl-3-crotyl-4-chloro-5-ethyl uracil are incorporated into an ointment base consisting of 3.0 g. of cetyl alcohol, 5.0 g. of anhydroud lanolin, and 82.0 g. of white petrolatum. The resulting ointment is applied to the virus-affected parts of the body.

Example 11

5.0 g. of 1-methyl-3-allyl-5-ethyl uracil are intimately mixed with 10.0 g. of glycine, 10.0 g. of lactose, and 75 g. of finely divided silicic acid sold under the trademark "Aerosil" are intimately mixed with each other to yield a virostatically effective powder.

EXAMPLE 12

1.0 g. of 1-methyl-crotlyl-5-ethyl uracil are mixed with 5.0 g. of ethanol and enclosed into a spray container with 94.0 g. of a propellant such as trichlorofluoro methane. The resulting preparation is applied by spraying to virus-affected parts of the body.

Example 13

5 g. of 1,5-diethyl-3-allyl-4-chloro uracil and 5 g. of a non-ionogenic emulsifier sold under the trademark "Cremophor EL" by Badische Anilin- & Soda-Fabrik of Ludwigshafen, Germany, which is a condensation product of ethylene oxide with castor oil, are intimately mixed with 90 cc. of physiological (0.9%) sodium chloride solution. The resulting mixture is repeatedly applied to the virus-affected parts of the body.

Example 14

2 g. of 1,5-diethyl-3-allyl-4-chloro uracil are emulsified with 2 g. of "Tween 60" sold by Atlas Powder Company of Wilmington and being a polyoxyethylene sorbitan mono-stearate, 6 g. of "Arlacel 60," sold by Atlas Powder Company of Wilmington, Del., and being a sorbitan mono-stearate, 10 g. of stearic acid, and 4 g. of "Witocan H," sold by Chemische Werke Witten G.m.b.H. of Witten (Ruhr), Germany, which is a mixture of fat-containing saturated fatty acids with 12 to 18 carbon atoms, in 76 cc. of distilled water. The resulting composition has proved of value in the treatment of virus infections.

Example 15

10 g. of 1,5-diethyl-3-allyl-4-chloro uracil are incorporated into an ointment of 10 g. petrolatum (Vaseline), 40 g. of anhydrous lanolin, 7 g. of liquid petrolatum (liquid paraffin), and 33 cc. of water. The resulting ointment is useful for topical application.

Of course, other solutions, lotions, ointments, powders, sprays, and the like compositions may be prepared with other solvents, ointment bases, excipients, and the like.

The composition containing the above mentioned substituted 5-ethyl uracil compounds according to the present invention are useful for topical application to the virus-affected parts of the human body. They may be applied not only to the skin of the patient but also to mucous membranes, such as the mucous membranes of the mouth and of the genital organs.

UTILITY

The virostatic activity of the substituted 5-ethyl uracil compounds according to the present invention has been

demonstrated in vitro in tissue cultures and in vivo on the rabbit's eye according to the method of Kaufman et al. "Arch. Ophthalm.," vol. 67 (1962), page 583. These tests have shown that said compounds are highly effective against DNA-viruses such as herpes, vaccinia, varicella virus as well as against RNA-viruses, such as foot-and-mouth-disease, Sindbis virus and others.

Clinical tests have been carried out especially with 1,5-diethyl-3-allyl-4-chloro uracil which was used in herpes diseases of the skin and the mucosa. The following Table II shows the results achieved by a treatment:

(a) with the composition according to Example 6,
(b) with the composition according to Example 7, and
(c) with the composition according to Example 8.

The preparations of these examples were applied externally by means of a swab stick to the respective parts of the body in the beginning of the treatment five times daily and later once to five times daily for a total period of from one day to five days. It may be mentioned that only patients who were suffering for more than three years from such herpes infections were treated with the preparations according to the present invention.

TABLE II

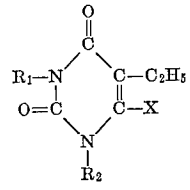
Ex.	Virus infection	Patients treated	Complete cure	Improvement	Irritation
6	*Herpes labialis*	8	6	2	0
6	*Herpes solaris*	1	----------	1	0
7	*Herpes labialis*	5	2	2	1
7	*Herpes simplex*	6	3	1	2
7	*Herpes genitalis*	2	2	0	0
7	*Stomatitis aphthosa*	2	1	1	0
8	*Herpes labialis*	8	6	2	0
8	*Herpes simplex*	3	2	1	0
8	*Herpes genitalis*	1	1	0	0
8	*Stomatitis aphthosa*	2	0	2	0
	Total	38	23	12	3

The rate of complete cure in these preliminary clinical tests thus is at least 60%. Treatment with the preparations according to the present invention has the advantage that the herpes blisters, for instance, of Herpes simplex became disiccated and healed within one to five days while without such a treatment healing required eight to ten days. It is to be assumed that irritation is not caused by the compounds of this invention but by the solvent dimethyl sulfoxide, especially since dimethyl sulfoxide applied without medicament to fresh Herpes blisters causes a burning sensation.

Of course, many changes and variations in the starting materials, unsaturated halogenides, and basic acid-burning agents used, in the reaction conditions, temperature, and duration, in the preparation and composition of pharmaceutical preparations containing the substituted 5-ethyl uracil compounds of the present invention, in the mode of administration and the amounts administered and the like may be made by those skilled in this art in accordance with the principles set forth herein and in the claimed annexed hereto.

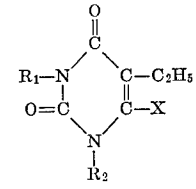
I claim:

1. A substituted 5-ethyl uracil compound of the formula:



wherein
R_1 is a member selected from the group consisting of alkyl with 1 to 4 carbon atoms, cyclohexyl, phenyl, tolyl, and benzyl;
R_2 is a member selected from the group consisting of allyl and crotyl; and
X is a member selected from the group consisting of hydrogen and halogen.

2. A substituted 5-ethyl uracil compound of the formula:



wherein
R_1 is a member selected from the group consisting of methyl and ethyl;
R_2 is a member selected from the group consisting of allyl and crotyl; and
X is a member selected from the group consisting of hydrogen and halogen.

3. The compound as defined in claim **1**, wherein X is chlorine.

4. The compound as defined in claim **1**, wherein R_1 is methyl.

5. The compound as defined in claim **1**, wherein R_1 is ethyl.

6. The compound as defined in claim **1**, wherein R_2 is allyl.

7. The compound as defined in claim **1**, wherein R_2 is crotyl.

8. The compound as defined in claim **1**, wherein R_1 is ethyl, R_2 is allyl, and X is chlorine, said compound being 1,5-diethyl-3-allyl-4-chloro uracil.

9. The compound as defined in claim **1**, wherein R_1 is methyl, R_2 is allyl, and X is chlorine, said compound being 1-methyl-3-allyl-4-chloro-5-ethyl-uracil.

10. The compound as defined in claim **1**, wherein R_1 is methyl, R_2 is crotyl, and X is chlorine, said compound being 1-methyl-3-crotyl-4-chloro-5-ethyl uracil.

11. The compound as defined in claim **1**, wherein R_1 is ethyl, R_2 is allyl, and X is hydrogen, said compound being 1,5-diethyl-3-allyl uracil.

12. The compound as defined in claim **1**, wherein R_1 is ethyl, R_2 is crotyl, and X is hydrogen, said compound being 1,5-diethyl-3-crotyl uracil.

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ALEX MAZEL, Primary Examiner

A. M. T. TIGHE, Assistant Examiner

U.S. Cl. X.R.

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