

XANTHATES AND THEIR THERAPEUTIC USE

The present invention relates to xanthate compounds, some of which are new, and to their therapeutic use.

Many xanthates are known, but it has been found that
5 certain xanthates exhibit beneficial anti-microbial and anti-viral effects as well as activities influencing cell growth.

Compounds of the invention, for therapeutic use, have the formula

10



wherein R^1 is benzyl, furyl, pyridyl, quinuclidinyl, C_{6-20} alkyl optionally substituted by hydroxy, C_{1-4}
15 alkoxy or halogen, or C_{3-20} cycloalkyl optionally substituted by hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl or halogen; and

R^2 is a mono- or polyvalent metal atom, 2,3-dihydroxypropyl, (C_{1-4} ω -hydroxyalkoxy)methyl, or C_{1-6}
20 alkyl optionally substituted by hydroxy, C_{1-4} alkoxy, amino or halogen.

C_{6-20} alkyl may be hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and pentadecyl, in straight, mono- or multiple-branch form,
25 preferably n-hexyl, n-decyl, n-dodecyl or n-tetradecyl. C_{3-20} cycloalkyl may be cyclopentyl, cyclohexyl, cycloheptyl, cyclo-octyl, cyclononyl, cyclodecyl, cycloundecyl, cyclodo-
decyl, cyclotridecyl, cyclotetradecyl or cyclopentadecyl,
30 preferably cyclohexyl or cyclododecyl; bi- and tricyclic groups are also included.

Halogen may be fluorine, chlorine, bromine or iodine. Chlorine and bromine are preferred halogen substituents.

R^1 is preferably furyl, pyridyl, quinuclidinyl,
35 C_{11-20} alkyl optionally substituted by hydroxy, C_{1-4}

alkoxy or halogen, or C₇₋₂₀ cycloalkyl optionally substituted by hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy or halogen. More preferably, R¹ is norbornyl, tricyclodecyl (preferred examples of which are adamantyl and tricyclo-
5 [5.2.1.0^{2,6}]decyl) or cyclododecyl.

R² may be a metal atom which is preferably monovalent. R² is most preferably an alkali metal such as sodium or potassium.

Particular examples of preferred compounds of the
10 invention, for therapeutic use, are alkali metal benzylxanthates, e.g. sodium benzylxanthate, alkali metal cyclohexylxanthates, e.g. sodium cyclohexylxanthate, and C₁₋₆ alkyl cyclohexylxanthates, e.g. methyl cyclohexylxanthate.

15 Novel compounds of the invention have the formula



wherein R³ is norbornyl, tricyclodecyl or cyclododecyl and R⁴ is a mono- or polyvalent metal atom.

R³ is preferably norbornyl, adamantyl, tricyclo-
20 [5.2.1.0^{2,6}]decyl or cyclododecyl. R⁴ is preferably an alkali metal.

Preferred novel compounds of the invention are alkali metal cyclododecylxanthates, e.g. sodium cyclododecylxanthate, alkali metal adamantylxanthates, e.g.
25 potassium adamantylxanthate, alkali metal 2-endo-bicyclo[2.2.1^{1,4}]heptylxanthates, e.g. potassium 2-endo-bicyclo[2.2.1^{1,4}]heptylxanthate, and alkali metal 8(9)-tricyclo[5.2.1.0^{2,6}]decylxanthates, e.g. potassium 8(9)-tricyclo[5.2.1.0^{2,6}]decylxanthate.

30 Compounds of the invention may be prepared by generally known methods, either by reacting an alcoholate of the formula R¹-O-M with carbon disulphide, or by reacting an alcohol of the formula R¹-OH with carbon

disulphide in the presence of a strong alkali, wherein R^1 is as defined above, e.g. as for R^3 , and M is an alkali metal. Such processes give compounds of the given formula in which R^2 (or R^4 in the particular case of the novel compounds) is an alkali metal. Such alkali metal xanthates may be converted to other compounds of the given formulae by reaction with a suitable alkylating agent.

Compounds of the invention are characterised by valuable pharmacodynamic properties, and may therefore be successful applied in human and veterinary medicine. Particular therapeutic uses for the compounds are anti-microbial, especially anti-viral, and anti-tumour. The anti-viral range of action comprises, for example, herpes, influenza and tumour viruses, while it has been found that the compounds can influence the growth of tumour cells. In particular, the compounds may be used as effective preventives of influenza and herpetic affections of the skin and mucous membrane. The compounds have relatively low toxicity.

The virustatic properties of compounds of the invention have been demonstrated by the in vitro testing of virus inhibition in an inhibition areola (plaque inhibition test) and by the plaque reduction method. The following virus strains were used: Influenza A2, Vaccine virus, Herpes virus and Tumour virus of the SV 40 type.

In the plaque inhibition test, tissues cultures of influenza and vaccine viruses (chick fibroblasts), parainfluenza (monkey renal epithelial cells) and herpes viruses (human amnion cells) are infected in such a manner that closely packed but individual plaques form. The test substance is then applied as a 1% (200 μ g 10.02 ml) solution, and the diameter of the inhibition areola (IA) is determined. The results are given in Table 1, where 0 indicates no IA, while +, ++ and +++ respectively

represent moderate (IA = 10-20 mm), good (IA = 20-30 mm) and very good (IA >30 mm) virustatic properties.

TABLE 1

Compound	Influenza Virus	Vaccine Virus	Herpes Virus
Sodium cyclododecyl- xanthate	+++	+++	+++
Sodium n-dodecylxanth- ate	+++	+++	+++
Sodium cyclo- hexylxanthate	++	+++	+++
Sodium benzyl- xanthate	+	+	+
Sodium 1-norbornyl- xanthate	++	+++	+++
Potassium 1-adamantyl- xanthate	+	+	+
1-aminoadaman- tane hydrochlor- ide (standard)	+++	0	0

5 In the plaque reduction test, the test substance is applied as a solution (20 µg/ml), and infection with the particular virus and incubation, the number of plaques produced by the virus is determined. The smaller the number of plaques is in comparison with the control, the more effective is the substance being tested. The
10 results are given in Table 2.

(16)

<u>TABLE 2</u>	
Compound	Plaque reduction (%)
Sodium cyclododecylxanthate	100
Sodium dodecylxanthate	100
Sodium cyclohexylxanthate	100
Standard aminoadamantane hydrochloride	10

Investigations, in vitro, by plaque reduction tests on various virus strains, showed growth inhibition at concentrations ranging from 1 to 100 µg/ml.

5 A pharmaceutical composition according to the invention comprises a compound of the invention in association with a physiologically acceptable excipient. In general, the diluent or carrier, i.e. excipient, may be a solid material or a liquid. Bland carriers are
10 preferred for some applications.

The composition can take the form of tablets, powders, capsules, liquid solutions, emulsions or suspensions, or other dosage forms which are particularly useful for oral administration. Liquid or semi-liquid
15 diluents may be employed for oral use. Such a medium can be, or contain a solvent such as, water. The only basic limitations of a liquid diluent are compatibility and palatability. The compositions can take the form of the selected xanthate admixed with solid diluents and/or
20 tableting adjuvants such as rice starch, corn starch, potato starch, lactose, saccharose, gelatin, talc, stearic acid, magnesium stearate, carboxymethylcellulose, gums such as gum acacia or tragacanth, chicle and agar agar. When in liquid form, the composition may be a
25 sterile or non-sterile solution, suspension, dispersion or elixir, as is well known in the art.

For topical application, the composition may be in, for example, solution, lotion, ointment, salve or tincture form. For parenteral, subcutaneous, intravenous, intramuscular or intraperitoneal administration, 5 the carrier is a sterile liquid such as water or oil, the oils being of vegetable, animal or synthetic origin. Glucose solutions are usually used for injectable solutions. In general, the injectable solutions contain 0.5 to 25% by weight of the active compound.

10 For oral administration, e.g. for the treatment of pneumonias, the compositions may be in vapour or spray form, for administration in the oronasal region. Best suited for oral administration are tablets, capsules, powders, solutions, suspensions and elixirs. Such 15 compositions should contain at least 2% w/w of the active compound.

For anti-viral use, the daily dosage of the active compound to be administered to adults during the course of the disease may be 5 to 100 mg per day. For oral 20 administration, a unit dosage generally contains 10 to 100, preferably about 50, mg of selected active ingredient. For parenteral administration in sterile solution, a unit dose usually contains 0.05 to 5, preferably about 2.5, mg of the active ingredient.

25 The following Examples illustrate how compounds of the invention may be prepared.

18

7

Example 1: Sodium cyclododecyl xanthate

100 g (0.54 mol) of cyclododecanol is heated to 100°C, 2.5 g (0.11 mol) of sodium is added, the temperature of the mixture being maintained at 220°C for 1 hour. The product is poured into a porcelain dish, pulverized after cooling, the powder being suspended in ether (400 ml), 9 g (0.12 mol) of carbon disulfide being added drop by drop. After the addition of 200 ml of water, the aqueous phase is separated, and 20 g of NaCl added. The precipitate is filtered and recrystallized twice from alcohol (120 ml).

Yield: 17 g (56% of the theoretical value)

Mp: 218 - 219°_{decomposition}

Elementary analysis

	calculated	found
C	55.32	54.42
H	8.16	8.08
S	22.69	21.90

In the same manner, the corresponding potassium salt is produced by employing potassium instead of sodium.

Example 2: Sodium benzyl xanthate

4.6 g (0.2 mol) of sodium is added to 108 g (1 mol) of benzyl alcohol under nitrogen. The mixture is heated to 160°C for 2 hours, poured into a porcelain dish, and allowed to cool. The semi-solid product is suspended in ether (400 ml), 15.2 g (0.2 mol) of carbon disulfide is added dropwise, and the mixture heated under reflux for 1 hour. The reaction solution is allowed to cool, the precipitate being filtered and washed with ether.

Yield: 16 g (39% of the theoretical value)

Mp: >180°_{decomposition}

Elementary analysis

	calculated	found	
C	42.86	43.05	(C ₈ H ₇ Na OS ₂ x H ₂ O)
H	4.02	4.31	
S	28.57	26.78	

19
In the same manner, the corresponding potassium salt is produced by employing potassium instead of sodium.

Example 3: Sodium cyclohexyl xanthate

3.6 g (0.16 mol) of sodium is added to 100 ml (1 mol) of cyclohexanol under nitrogen, and heated under reflux until complete reaction of the sodium has taken place. The reaction solution is poured into a porcelain dish and pulverized after cooling. The powder is suspended in ether (400 ml) and heated to reflux for 15 min. After cooling, 12.8 g (0.17 mol) of carbon disulfide is added dropwise. After the addition of 200 ml of water, the aqueous phase is separated, and 40 g of NaCl added. The precipitate is filtered, washed with ether and dried.

Yield: 25 g (75% of the theoretical value)

Mp: $>200^{\circ}$ decomposition

Elementary analysis

	calculated	found
C	42.42	42.21
H	5.55	5.52
S	32.32	31.87

In the same manner, the corresponding potassium salt is produced by employing potassium instead of sodium.

In the same manner, starting from n-hexanol, the corresponding sodium and potassium n-hexyl xanthates are prepared and found to be active virustatic agents.

Example 4: Cyclohexyl methyl xanthate

3 g (0.015 mol) of sodium cyclohexyl xanthate is dissolved in 50 ml of dried methanol and heated to reflux with 10.7 g (0.075 mol) of methyl iodide for 1 hour. After cooling, the reaction solution is evaporated by using a rotary evaporator, dissolved in ether/water (50/50), the ether phase being separated and dried with sodium sulfate, purified with active carbon/bleaching earth, and evaporated with the aid of a rotary evaporator.

Yield: 2 g (70% of the theoretical value)

Elementary analysis

	calculated	found
C	50.52	50.47
H	7.36	7.28

Example 5: Potassium adamantyl xanthate

15.2 g (0.1 mol) of adamantanol is dissolved in dried tetrahydrofuran, nitrogen is introduced into the solution and 2 g of potassium (0.05 mol) is added. The solution is heated under reflux for 10 hours. After cooling, the product is suspended in 200 ml of ether and heated to reflux for 15 minutes. 3.8 g (0.05 mol) of carbon disulfide is added, and the solution is heated again for 45 minutes under reflux. After cooling, 200 ml of water is added. The aqueous phase is separated, 25 g of NaCl added, and the precipitate filtered.

Yield: 2 g (8% of the theoretical value)

Mp: $>300^{\circ}$ decomposition

Elementary analysis

	calculated	found
C	49.60	49.82
H	5.63	5.56
S	24.05	23.50

In the same manner, the corresponding sodium salt is produced by employing sodium instead of potassium.

Example 6: Potassium 2-endo-bicyclo[2.2.1^{1,4}]-heptyl xanthate

340 g (about 3 mol) of endo-norborneol is melted (160°C) under nitrogen atmosphere and reacted in portions with a total of 19.55 g (0.5 mol) of crust-free potassium. The temperature is maintained at 160° until complete dissolution of the metal has taken place. Subsequently, excess norborneol is distilled off, the colorless residue dried under high vacuum for a short time, and dissolved in 500 ml of absolute tetrahydrofuran. With cooling, 31 ml (0.5 mol) of carbon disulfide - dissolved in 150 ml of absolute ether - is added to this alcoholate drop by drop. The reaction mixture is stirred for 1 hour at 40°C . The xanthate separating already in the course of the reaction as a pale yellow precipitate is precipitated to a large extent by the addition of 1 l of dry ether. The precipitate is suction filtered and thoroughly rinsed with ether on the suction filter apparatus.

10

The xanthate crystallizes from concentrated alcoholic solution by forming fine, pale yellow needles.

Yield: 95 g (83% of the theoretical value)

Mp: 256 - 258^o decomposition

Elementary analysis

	calculated	found
C	42.44	42.40
H	4.90	4.92
S	28.32	27.90

In the same manner, the corresponding sodium salt is produced by employing sodium instead of potassium.

Example 7: Potassium 8(9)-tricyclo[5.2.1.0^{2,6}]decyl xanthate

457 g (about 3 mol) of tricyclo[5.2.1.0^{2,6}] decanol-8(9) (TCD alcohol A, isomer mixture distributed by Hoechst AG) is reacted under protective gas atmosphere (nitrogen) in portions with a total of 19.55 g (0.5 mol) of crust-free potassium with stirring at 150-160^oC. The temperature of the mixture is kept at this level until complete reaction of the metal has taken place. Subsequently, excess alcohol is distilled off under vacuum, the alcoholate being dried under high vacuum and dissolved in 500 ml of absolute tetrahydrofuran. With cooling, 31 ml (0.5 mol) of carbon disulfide in 150 ml of absolute ether is gradually added to the reaction solution. The mixture is stirred for 1 hour at 40^oC, the xanthate is precipitated by adding 1 l of dry ether, suction filtered and thoroughly rinsed with ether on the suction filter apparatus. After recrystallization from ethanol, fine pale yellow crystals are obtained.

Yield: 104 g (78% of the theoretical value)

Mp: 260^o decomposition

Elementary analysis

	calculated	found
C	49.58	49.60
H	5.67	5.62
S	24.07	24.19

CLAIMS

1. A compound, for therapeutic use, which has the formula

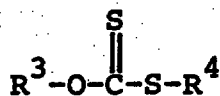


- wherein R^1 is benzyl, furyl, pyridyl, quinuclidinyl, C_{6-20} alkyl optionally substituted by hydroxy, C_{1-4} alkoxy or halogen, or C_{3-20} cycloalkyl optionally substituted by hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl or halogen; and
- R^2 is a mono- or polyvalent metal atom, 2,3-dihydroxypropyl, (C_{1-4} ω -hydroxyalkoxy)methyl, or C_{1-6} alkyl optionally substituted by hydroxy, C_{1-4} alkoxy, amino or halogen.
2. A compound of claim 1, wherein R^2 is an alkali metal.
3. A compound of claim 1 or claim 2, wherein R^1 is furyl, pyridyl, quinuclidinyl, C_{11-20} alkyl optionally substituted by hydroxy, C_{1-4} alkoxy or halogen, or C_{7-20} cycloalkyl optionally substituted by hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy or halogen.
4. A compound of claim 3, wherein R^1 is norbornyl, tricyclodecyl or cyclododecyl.
5. A compound of claim 4, wherein R^1 is norbornyl, adamantyl, tricyclo[5.2.1.0^{2,6}]decyl or cyclododecyl.
6. An alkali metal benzylxanthate or cyclohexylxanthate, for therapeutic use.
7. Sodium benzylxanthate or cyclohexylxanthate, for therapeutic use.
8. A C_{1-6} alkyl cyclohexylxanthate, for therapeutic use.
9. Methyl cyclohexylxanthate, for therapeutic use.
10. A compound of the formula

22



12



wherein R^3 is norbornyl, tricyclodecyl or cyclododecyl and R^4 is a mono- or polyvalent metal atom.

11. A compound of claim 10, wherein R^4 is an alkali metal.
12. A compound of claim 10 or claim 11, wherein R^3 is norbornyl, adamantyl, tricyclo[5.2.1.0^{2,6}]decyl or cyclododecyl.
13. An alkali metal cyclododecylxanthate, adamantylxanthate, 2-endo-bicyclo[2.2.1^{1,4}]heptylxanthate or 8(9)-tricyclo[5.2.1.0^{2,6}]decylxanthate.
14. Sodium cyclododecylxanthate, potassium adamantylxanthate, potassium 2-endo-bicyclo[2.2.1^{1,4}]heptylxanthate, or potassium 8(9)-tricyclo[5.2.1.0^{2,6}]decylxanthate.
15. A compound of any of claims 10 to 14, for therapeutic use.
16. A compound of any of claims 1 to 14, for antiviral use.
17. A compound of any of claims 1 to 14, for antitumour use.
18. A pharmaceutical composition which comprises a compound of any preceding claim, in association with a physiologically acceptable excipient.
19. A process for preparing a compound of claim 10 when R^4 is an alkali metal, which comprises reacting an alcoholate of the formula $\text{R}^3\text{-O-M}$, wherein R^3 is as defined in claim 10 and M is an alkali metal, with carbon disulfide.
20. A process for preparing a compound of claim 10 when R^4 is an alkali metal, which comprises reacting an alcohol of the formula $\text{R}^3\text{-OH}$, wherein R^3 is as defined in claim 10, with carbon disulfide in the presence of strong alkali.