United States Patent Office

3,574,185

Patented Apr. 6, 1971

3,574,185

ACYL DERIVATIVES OF ERYTHROMYCIN OXIME

Zrinka Tamburasev, Gabrijela S. Vazdar-Kobrehel, and Slobodan Djokic, Zagreb, Yugoslavia, assignors to PLIVA Pharmaceutical and Chemical Works, Zagreb, Yugoslavia

No Drawing. Filed July 16, 1968, Ser. No. 745,104
Claims priority, application Yugoslavia, Aug. 3, 1967, 1,540/67
Int. Cl. C07c *47/18*
U.S. Cl. 260—210 16 Claims

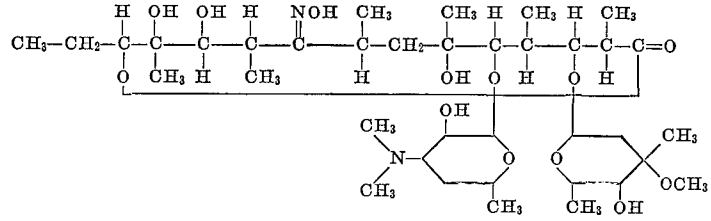
ABSTRACT OF THE DISCLOSURE

Mono- and bis-carboxylic acid acylates of erythromycin oxime, useful as antibiotics.

The present invention relates to acyl derivatives of erythromycin oxime and to the preparation thereof.

It is known that acylation of erythromycin with different acid chlorides or acid anhydrides yields a variety of products with a single acyl grouping attached to the hydroxyl group of the desosaminyl moiety. The sole exception is with the use of acetic anhydride as an acylating agent, which yield erythromycin diacetate. Some erythromycin esters, such as propionate, ethylsuccinate, ethylcarbonate, have been recommended in therapeutic practice owing to their advantages over erythromycin itself.

Since erythromycin oxime of the formula



possesses one additional group (oximino) which can be acylated it is possible to prepare mono- and bis-acyl derivatives thereof.

It has been found that mono- and bis-acyl derivatives can be prepared by the reaction of erythromycin oxime with acid chlorides of aliphatic and aromatic mono-carboxylic acids of the formula RCOCl wherein R is an alkyl radical of 2 to 17 carbon atoms or a phenyl radical, with chlorides of dicarboxylic acid esters of the formula $ClOC(CH_2)_nCOOR'$ wherein R' is a lower alkyl radical (methyl, ethyl) and *n* is 1 to 4, in the presence of an alkali metal salt, such as sodium bicarbonate. If this acylation is carried out in an inert anhydrous solvent, such as acetone, using an equivalent quantity or a small excess of the acylating agent in the presence of an alkali metal salt at room temperature, exclusively mono-acyl derivatives can be obtained. With a slight excess over two equivalents of the acylating agent in the presence of the double amount of an alkali metal salt in the solution of same inert anhydrous solvent at elevated temperature, corresponding bis-acyl derivatives are formed.

The antibiotic activities of the obtained mono- and bis-acyl derivatives, determined on Bacillus subtilis and Bacillus mycoides, are listed in Table I.

TABLE I. —ACYL DERIVATIVES OF ERYTHROMYCIN OXIME

Acyl radical:	Antibiotic activity U/mg.
Mono-propionate	500–550
Mono-palmitate	(1)
Mono-stearate	(1)
Mono-benzoate	(1)
Mono-methylsuccinate	400–450
Mono-ethylsuccinate	250–300
Mono-methyladipate	400–450
Mono-ethyladipate	350–400
Bis-propionate	200–250
Bis-palmitate	(1)
Bis-stearate	(1)
Bis-benzoate	(1)
Bis-methylsuccinate	400–450
Bis-ethylsuccinate	200–250
Bis-methyladipate	400–450
Bis-ethyladipate	200–250

[1] In traces.

From the above table it can be seen that the acyl derivatives prepared by us with chlorides of aliphatic and aromatic mono-carboylic acids, erythromycin oxime propionates are highly active. All acyl derivatives prepared with chlorides of aliphatic dicarboxylic acid esters possess well defined antibiotic activity.

The following example, in which the novel acyl derivatives of erythromycin oxime are provided by the invention, is given by way of illustration:

EXAMPLE 1

Erythromycin oxime mono-propionate

To a suspension of 5 g. (6.67 millimols) of erythromycin oxime in 100 ml. of dry acetone, 2.5 g. of dry sodium bicarbonate were added. Then, the solution of 0.790 g. (8.8 millimols) of propionyl chloride in 25 ml. of dry acetone was added dropwise with stirring over a period of one hour. After stirring for one additional hour, the reaction mixture was filtered, the filtrate diluted with a solution of 2.5 g. sodium bicarbonate in 130 ml. water and extracted with one 100 ml. and two 50 ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and freed from ether in vacuo. For analysis, the substance was purified by dissolution in acetone and addition of water persistent turbidity. After standing for three hours, crystallisation set in. The yield was 3.92 g. (73%), M.P. 126–129° C.

Analysis.—Calculated for $C_{40}H_{72}N_2O_{14}$ (percent): C, 59.63; H, 6.02; N, 3.48. Found (percent): C, 59.23; H, 6.18; N, 3.21.

EXAMPLE 2

Erythromycin oxime mono-palmitate

From 5 g. (6.67 millimols) of erythromycin oxime, 2.375 g. (8.64 millimols) of palmitoyl chloride and 2.5 g. of sodium bicarbonate, by the process described in Example 1, there are obtained 5.2 g. (78.8%) of mono-palmitate, M.P. 88–92° C.

Analysis.—Calculated for $C_{53}H_{98}N_2O_{14}$ (percent): C, 64.47; H, 10.01; N, 2.84. Found (percent): C, 64.28; H, 10.21; N, 2.48.

EXAMPLE 3

Erythromycin oxime mono-stearate

From 5 g. (6.67 millimols) of erythromycin oxime, 2.616 g. (8.64 millimols) of stearoyl chloride and 2.5 g. of sodium bicarbonate, by the process described in Example 1, there are obtained 5.24 g. (77.49%) of mono-stearate, M.P. 74–78° C.

Analysis.—Calculated for $C_{55}H_{102}N_2O_{14}$ (percent): C, 65.05; H, 10.12; N, 2.76. Found (percent): C, 65.32; H, 10.33; N, 2.91.

EXAMPLE 4

Erythromycin oxime mono-benzoate

From 5 g. (6.67 millimols) of erythromycin oxime, 1.26 g. (8.64 millimols) of benzoyl chloride and 2.5 g. of sodium carbonate, by the process described in Example 1, there are obtained 4.15 g. (73%) of mono-benzoate, M.P. 150–152° C.

Analysis.—Calculated for $C_{44}H_{72}N_2O_{14}$ (percent): C, 61.95; H, 8.53; N, 3.28. Found (percent): C, 61.72; H, 8.28; N, 3.36.

EXAMPLE 5

Erythromycin oxime mono-methylsuccinate

From 5 g. (6.67 millimols) of erythromycin oxime, 1.008 g. (6.67 millimols) of succinic methylester chloride and 2.5 g. of sodium bicarbonate, by the process described in Example 1, there are obtained 4.1 g. (70.9%) of mono-methylsuccinate, M.P. 108–112° C.

Analysis.—Calculated for $C_{42}H_{74}N_2O_{16}$ (percent): C, 58.45; H, 8.76; N, 3.25. Found (percent): C, 58.60; H, 8.70; N, 3.54.

EXAMPLE 6

Erythromycin oxime mono-ethylsuccinate

From 5 g. (6.67 millimols) of erythromycin oxime, 1.098 g. (6.67 millimols) of succinic acid ethylester chloride and 2.5 g. of sodium bicarbonate, by the process described in Example 1, there are obtained 4.23 g. (72.5%) of mono-ethylsuccinate, M.P. 99–102° C.

Analysis.—Calculated for $C_{43}H_{76}N_2O_{16}$ (percent): C, 58.83; H, 8.74; N, 3.19. Found (percent): C, 58.57; H, 9.14; N, 3.38.

EXAMPLE 7

Erythromycin oxime mono-methyladipate

From 5 g. (6.67 millimols) of erythromycin oxime, 1.19 g. (6.67 millimols) of adipic acid methylester chloride and 2.5 g. of sodium bicarbonate, by the process described in Example 1, there are obtained 4.5 g. (76%) of mono-methyladipate, M.P. 89–94° C.

Analysis.—Calculated for $C_{44}H_{78}N_2O_{16}$ (percent): C, 59.30; H, 8.82; N, 3.14. Found (percent): C, 59.06; H, 8.60; N, 3.24.

EXAMPLE 8

Erythromycin oxime mono-ethyladipate

From 5 g. (6.67 millimols) of erythromycin oxime, 1.28 g. (6.67 millimols) of adipic acid mono-ethylester chloride and 2.5 g. of sodium bicarbonate, by the process described in Example 1, there are obtained 4.8 g. (79.3%) of mono-ethyladipate, M.P. 82–86° C.

Analysis.—Calculated for $C_{45}H_{80}N_2O_{16}$ (percent): C, 59.71; H, 8.91; N, 3.10. Found (percent): C, 59.52; H, 8.66; N, 3.01.

EXAMPLE 9

Erythromycin oxime bis-propionate

To a suspension of 5 g. (6.67 millimols) of erythromycin oxime in 100 ml. of dry acetone, 5.0 g. of dry sodium bicarbonate were added. Then the solution of 1.596 g. (17.29 millimols) of propionyl chloride in 50 ml. of dry acetone was added dropwise with stirring over a period of one hour. Stirring was continued for 8 hours more while heating the reaction mixture under reflux. After cooling to room temperature and filtration, the clear filtrate was diluted with a solution of 5 g. sodium bicarbonate in 250 ml. water and extracted with one 100 ml. and two 50 ml. portions of ether. The isolation of the product was performed in the same manner as described in Example 1. The yield was 4.49 g. (78.2%), M.P. 196–202° C.

Analysis.—Calculated for $C_{43}H_{76}N_2O_{15}$ (percent): C, 59.97; H, 8.90; N, 3.25. Found (percent): C, 59.36; H, 8.71; N, 3.34.

EXAMPLE 10

Erythromycin oxime bis-palmitate

From 5 g. (6.67 millimols) of erythromycin oxime, 4.5 g. (16.38 millimols) of palmitoyl chloride and 5 g. of sodium bicarbonate, by the process described in Example 9, there are obtained 6.31 g. (77%) of bis-palmitate, M.P. 68–72° C.

Analysis.—Calculated for $C_{69}H_{128}N_2O_{15}$ (percent): C, 67.71; H, 10.52; N, 2.29. Found (percent): C, 68.11; H, 10.41; N, 2.66.

EXAMPLE 11

Erythromycin oxime bis-stearate

From 5 g. (6.67 millimols) of erythromycin oxime, 5 g. (16.52 millimols) of stearoyl chloride and 5 g. of sodium bicarbonate, by the process described in Example 9, there are obtained 6.2 g. (72.6%) of bis-stearate, M.P. 63.5–66.5° C.

Analysis.—Calculated for $C_{73}H_{136}N_2O_{15}$ (percent): C, 68.40; H, 10.70; N, 2.18. Found (percent): C, 68.57; H, 10.55; N, 2.22.

EXAMPLE 12

Erythromycin oxime bis-benzoate

From 5 g. (6.67 millimols) of erythromycin oxime, 2.52 g. (17.28 millimols) of benzoyl chloride and 5 g. of sodium bicarbonate, by the process described in Example 9, there are obtained 4.75 g. (74%) of bis-benzoate, M.P. 193–196° C.

Analysis.—Calculated for $C_{51}H_{76}N_2O_{15}$ (percent): C, 64.00; H, 8.01; N, 2.92. Found (percent): C, 64.21; H, 8.19; N, 2.86.

EXAMPLE 13

Erythromycin oxime bis-methylsuccinate

From 5 g. (6.67 millimols) of erythromycin oxime, 2.424 g. (16.1 millimols) of succinic acid methylester chloride, and 5 g. of sodium bicarbonate, by the process described in Example 9, there are obtained 5.18 g. (79.5%) of bis-methylsuccinate, M.P. 173–176° C.

Analysis.—Calculated for $C_{47}H_{80}N_2O_{19}$ (percent): C, 57.74; H, 8.25; N, 2.86. Found (percent): C, 57.55; H, 8.55; N, 3.16.

EXAMPLE 14

Erythromycin oxime bis-ethylsuccinate

From 5 g. (6.67 millimols) of erythromycin oxime, 2.649 g. (16.1 millimols) of succinic acid ethylester chloride and 5 g. of sodium in carbonate, by the process described in Example 9, there are obtained 4.92 g. (73.4%) of bis-ethylsuccinate, M.P. 160–162° C.

Analysis.—Calculated for $C_{49}H_{84}N_2O_{19}$ (percent): C, 58.54; H, 8.42; N, 2.78. Found (percent): C, 58.31; H, 8.20; N, 2.93.

EXAMPLE 15

Erythromycin oxime bis-methyladipate

From 5 g. (6.67 millimols) of erythromycin oxime, 2.86 g. (16.1 millimols) of adipic acid methylester chloride and 5 g. of sodium bicarbonate, by the process described in Example 9, there are obtained 5.25 g. (76.2%) of bis-methyladipate, M.P. 78–83° C.

Analysis.—Calculated for $C_{51}H_{88}N_2O_{19}$ (percent): C, 59.28; H, 8.59; N, 2.71. Found (percent): C, 59.23; H, 8.83; N, 3.00.

EXAMPLE 16

Erythromycin oxime bis-ethyladipate

From 5 g. (6.67 millimols) of erythromycin oxime, 3.1 g. (16.1 millimols) of adipic acid ethylester chloride and 5 g. of sodium bicarbonate, by the process described in Example 9, there are obtained 5.68 g. (80.1%) of bis-ethyladipate, M.P. 72–76° C.

Analysis.—Calculated for $C_{53}H_{92}N_2O_{19}$ (percent): C, 59.89; H, 8.17; N, 2.64. Found (percent): C, 60.25; H, 8.30; N, 2.90.

What we claim is:

1. Erythromycin oxime mono-propionate.
2. Erythromycin oxime mono-palmitate.

3. Erythromycin oxime mono-stearate.
4. Erythromycin oxime mono-benzoate.
5. Erythromycin oxime mono-methylsuccinate.
6. Erythromycin oxime mono-ethylsuccinate.
7. Erythromycin oxime mono-methyladipate.
8. Erythromycin oxime mono-ethyladipate.
9. Erythromycin oxime bis-propionate.
10. Erythromycin oxime bis-palmitate.
11. Erythromycin oxime bis-stearate.
12. Erythromycin oxime bis-benzoate.
13. Erythromycin oxime bis-methylsuccinate.
14. Erythromycin oxime bis-ethylsuccinate.
15. Erythromycin oxime bis-methyladipate.
16. Erythromycin oxime bis-ethyladipate.

References Cited

UNITED STATES PATENTS

2,862,921	12/1958	Booth et al.	260—210E
2,967,129	1/1961	Clark, Jr.	260—210E
2,993,833	7/1961	Stephens	260—210E
3,014,027	12/1961	Druey et al.	260—211

LEWIS GOTTS, Primary Examiner

J. R. BROWN, Assistant Examiner

U.S. Cl. X.R.

424—180

PO-1050
(5/69)

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,574,185 Dated April 6, 1971

Inventor(s) Zrinka Tamburasev, Gabrijela S. Vazdar-Kobrehel and Slobodan Kjokic

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Col. 2, line 60: before "persistent" insert --until--.

Col. 4, line 73: correct "sodium in carbonate" to read --sodium bicarbonate--.

Signed and sealed this 13th day of July 1971.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

WILLIAM E. SCHUYLER, JR.
Commissioner of Patents