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Note

Erythromycin Series. III*. Acylation of Erythromycin Oxime and 9-Amino-3-*O*-cladinosyl-5-*O*-desosaminyl-6,11,12-trihydroxy-2,4,6,8,10,12-hexamethylpentadecane-13-olide with Chlorides of Some Alyphatic Monocarboxylic Acids

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In our previous publication[1] the preparation of mono- and bis-acyl compounds derived from erythromycin oxime and 9-amino-3-*O*-cladinosyl-5-*O*-desosaminyl-6,11,12-trihydroxy-2,4,6,8,10,12-hexamethylpentadecane - 13 - olide (erythromycyl amine) and methyl resp. ethyl ester chlorides of succinic and adipic acid was described. It was found that neither monoacylation nor diacylation effected a substantial change in the antibiotic activity of the starting compounds. The sole exception were ethyl succinates and adipates where a lower activity was found. This is in complete agreement with the relative antibiotic activity of erythromycin and its corresponding esters (methyl- or ethylsuccinate resp. adipate).

In continuation of our work on acylation of erythromycin oxime and erythromycyl amine we have prepared a series of hitherto undescribed mono- and bis-acyl derivatives by action of acid chlorides of propionic, palmitic and stearic acid.

Formulas, molecular weights and physical properties of the compounds prepared are presented in Table I along with their antibiotic activity determined by the plate bioassay method. Comparing these results with those for corresponding erythromycin esters resp. starting compounds (see Table II) the following can be concluded: The activity of erythromycin oxime propionate is equal to the activity of the oxime itself, as in the case with erythromycin and its propionate. The activity of erythromycylamine propionate is, however, somewhat lower then that of its parent compound. A still more marked drop of activity was found with bis-propionates of the oxime and the amine. Acyl derivatives of erythromycin oxime and erythromycyl amine with palmitic and stearic acid are inactive which is also the case with corresponding erythromycin esters.

The general method for the preparation of these compounds was described in the preceding publication[1].

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* Part II.: Z. Tamburašev, G. Vazdar, and S. Djokić, *Croat. Chem. Acta* **39** (1967) 273.

TABLE I

The Physical Properties and Plate Bioassay of O- *and* N-*Acyl Derivatives*

No.	Compound	Formula Mol. weight	m. p.[a] °C	$[\alpha]_D^{20}$[b]	*pK*[c]	Activity by plate bioassay[d] u/mg
I	Erythromycin oxime propionate	$C_{40}H_{72}N_2O_{14}$ 805.03	126—129	— 120	7.23	521
II	Erythromycin oxime bis-propionate	$C_{43}H_{76}N_2O_{15}$ 861.09	196—202	— 133	5.92	240
III	Erythromycin oxime palmitate	$C_{53}H_{98}N_2O_{14}$ 987.30	88—92	— 93.5	7.4	traces
IV	Erythromycin oxime bis-palmitate	$C_{69}H_{128}N_2O_{15}$ 1225.71	68—72	— 71.5	5.8	traces
V	Erythromycin oxime stearate	$C_{55}H_{102}N_2O_{14}$ 1015.37	74—78	— 99.6	7.5	traces
VI	Erythromycin oxime bis-stearate	$C_{73}H_{136}N_2O_{15}$ 1281.83	63—66	— 65	6.1	traces
VII	Erythromycyl amine propionate	$C_{40}H_{74}N_2O_{13}$ 791.04	122—126	— 100	6.52	330
VIII	Erythromycyl amine bis-propionate	$C_{43}H_{78}N_2O_{14}$ 847.11	194—195	— 125	5.73	200
IX	Erythromycyl amine palmitate	$C_{53}H_{100}N_2O_{13}$ 974.34	62—67	— 84.1	7.3	traces
X	Erythromycyl amine bis-palmitate	$C_{69}H_{130}N_2O_{14}$ 1211.73	65—67	— 63.1	5.7	traces
XI	Erythromycyl amine stearate	$C_{55}H_{104}N_2O_{13}$ 1001.38	63—66	— 84.6	7.2	traces
XII	Erythromycyl amine bis-stearate	$C_{73}H_{138}N_2O_{14}$ 1267.85	61—63	— 60.0	5.9	traces

All compounds gave satisfactory C, H, and N analyses.

[a] Fischer-Jones apparatus; [b] 2% in acetone; [c] 66% dimethylformamide-water; [d] *British Pharmacopoeia* 1963, p. 1102.

TABLE II

The Physical Properties and Plate Bioassay of Erythromycin, Oxime, Amino Compound and of Some Erythromycin Esters

Compound	Ref.	m. p. °C	$[\alpha]_D^{20}$	*pK*	Activity by Plate bioassay u/mg
Erythromycin	2	135—140	— 73.5	8.6	
	3		— 78.0		
	4				949
Erythromycin oxime	5	184—189	— 73.5	—	520
Erythromycyl amine	5	145—148	— 50.0	8.4	480
Erythromycin propionate	6	122—126	— 81.6	6.9	928
Erythromycin palmitate	7	73—76	—	6.7	0
Erythromycin stearate	8	73—75	— 41.7	—	3

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IZVOD

Studije u redu eritromicina. III. Aciliranje eritromicin oksima i 9-amino-3-*O*-kladinozil-5-*O*-desozaminil-6,11,12-trihidroksi-2,4,6,8,10,12-heksametilpentadekan-13-olida s kloridima nekih alifatskih kiselina

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Reakcijom eritromicin oksima i eritromicil amina s kloridima propionske, palmitinske i stearinske kiseline pripravljeni su odgovarajući mono- i bis-acil derivati (I—XII, Tabela I). Uspoređujući vrijednosti za antibiotsku aktivnost ovih spojeva s odgovarajućim esterima eritromicina i njihovim matičnim supstancama (Tabela II), može se vidjeti da eritromicin oksim propionat ima isti aktivitet kao i sam oksim. Isti je slučaj i kod eritromicina i njegova propionata. Međutim, aktivitet eritromicil amin propionata je nešto niži od njegove matične supstance. Još značajniji pad aktiviteta nalazimo kod bis-propionata kako oksima tako i amina. Acil derivati oksima i amina s palmitinskom i stearinskom kiselinom nisu aktivni jednako kao i odgovarajući esteri eritromicina.

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