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ERYTHROMYCIN STUDY: 9-AMINO-3-O-CLADINOSYL-5-O-DESOSAMINYL-6,11,12-TRYHYDROXY-2,4,6,8,10,12-HEXAMETHYLPENTADECANE-13-OLIDE

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IN reduction of erythromycin (I) to dihydroerythromycin (VI) the keto carbonyl in position 9 of the aglycon part of the molecule was transformed into a hydroxyl group.[1,2] No other reactions involving specific changes in keto group of I are described. Attempts to prepare the usual carbonyl derivatives of erythromycin failed until now. In reaction with hydrazine erythromycin yielded neither the expected hydrazone nor a hydrazide. Only partial structure for the product of this reaction was proposed.[2] Since dihydroerythromycin is biologically inactive, it is supposed that the keto group is one of the decisive factors for antibiotic activity of erythromycin.

In order to get a better insight in the influence of the keto group of I on its antibiotic activity, the reaction of erythromycin with hydroxylamine was performed. The reaction was carried out with hydroxylamine hydrochloride in methanol in the presence of barium carbonate under anhydrous condi-

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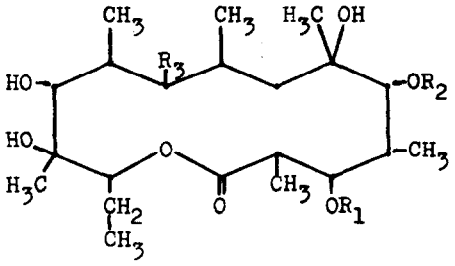
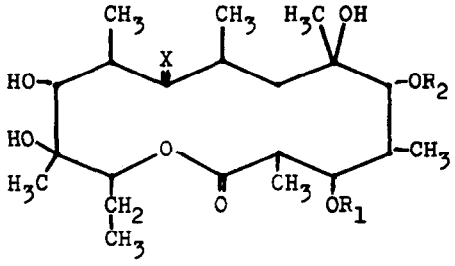
[1] E.H.Flynn, M.V.Sigal, Jr., P.F.Wiley and K.Gerzon, J.Am.Chem.Soc. 76, 3121 (1954)

[2] M.V.Sigal, Jr., P.F.Wiley, K.Gerzon, E.H.Flynn, V.C.Quarck and O.Weaver, J.Am. Chem.Soc. 78, 388(1956)

tions.[3] From the reaction mixture erythromycin oxime (II) was isolated in about 50 % yield. After recrystalization from absolute methanol the compound had a m.p. 184-189° (dec.), $[\alpha]_D^{25}$= -73,5° (c= 1% in methanol), $C_{37}H_{68}N_2O_{13}$.* In the infra-red spectra the original carbonyl band at 5,9[1] disappeared but





I	R_1= cladinosyl,	R_2= desosaminyl,	X= O
II	R_1= cladinosyl,	R_2= desosaminyl,	X= NOH
III	R_1= cladinosyl,	R_2= desosaminyl,	R_3= NH_2
IV	R_1= H,	R_2= desosaminyl,	R_3= NH_2
V	R_1= H,	R_2= H,	R_3= NH_2
VI	R_1= cladinosyl,	R_2= desosaminyl,	R_3= OH
VII	R_1= H,	R_2= desosaminyl,	R_3= OH
VIII	R_1= H,	R_2= H,	R_3= OH

a new absorption band at 6,15 considered as being typical for -C=N-[4,5] is present. By reduction of II with sodium borohydride the 9-amino-3-O-cladinosyl-5-O-desosaminyl-6,11,12-trihydroxy-2,4,6,8,10,12-hexamethylpentadecane-13-olide (III) was obtained in 70% yield, m.p. 142-147°, $[\alpha]_D^{25}$= -50° (c= 1%

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[3] L.C.Cheney and J.R.Piening, J.Am.Chem.Soc. 67,731(1945)

* All new compounds gave satisfactory analyses

[4] F.W.L.Gass and F.W.Bope, J.Am.Pharm.Assoc. 48,186(1949)

[5] M.M.Randall,N.Fuson,R.G.Fowler and J.R.Dangl, Infrared Determination of Organic Structures p. 5, D. Van Nostrand Co., New York, Toronto, London (1952)

in methanol), $C_{37}H_{70}N_2O_{12}$. Dipicrate m.p. 185-187°, $C_{49}H_{76}N_8O_{26}$. Dihydrochloride m.p. 142-144°, $C_{37}H_{72}O_{12}Cl_2$.

In order to show with certainty that III has the structure proposed, the following reactions were carried out. Hydrolysis of III with 1% hydrochloric acid solution in methanol at room temperature yielded 9-amino-5-O-desosaminyl-3,6,11,12-tetrahydroxy-2,4,6,8,10,12-hexamethylpentadecane-13-olide (IV), m.p. 157-162°, $/\alpha/_D^{25} = -35°$ (c= 1% in methanol), $C_{29}H_{56}N_2O_9$. By hydrolysis of IV with 2N hydrochloric acid at 60° 9-amino-3,5,6,11,12-pentahydroxy-2,4,6,8,10,12-hexamethylpentadecane-13-olide (V) was obtained, m.p. 108-115°, $/\alpha/_D^{25} = +35°$ (c= 1% in methanol), $C_{21}H_{41}NO_7$. Picrate, m.p. 115-118°, $C_{27}H_{44}N_4O_{14}$. Reaction of V with sodium nitrite followed by hydrolysis gave the compound identical in all respects with "dehydration product A" prepared by Sigal and coworkers from VII or VIII.[2]

The assay for the antibiotic activity of erythromycin oxime and 9-amino-3-O-cladinosyl-5-O-desosaminyl-6,11,12-trihydroxy-2,4,6,8,10,12-hexamethyl pentadecane-13-olide on Bacillus subtilis and Bacillus mycoides showed that the first possesses an activity of 500-550 U/mg, and second 460-500 U/mg respectively. This indicates that oximation of the keto group and reduction of the oxime did not effect a loss of antibiotic activity as it was the case after the reduction of the keto group.

The above compounds and their derivatives are under further studies in our laboratory.

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