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LINCOMYCIN. XIII. N-DEALKYLATION OF LINCOMYCIN AND ITS ANALOGS

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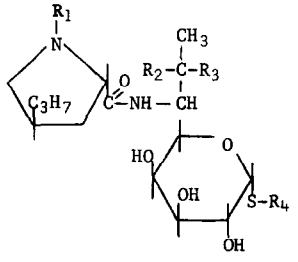
One phase of a research program directed toward the modification of the antibiotics lincomycin (1)[1] and clindamycin (2)[2] required the preparation of 1'-demethyl analogs. 1'-Demethyllincomycin (3)[3] was first obtained in low yield by incubation of *Streptomyces*



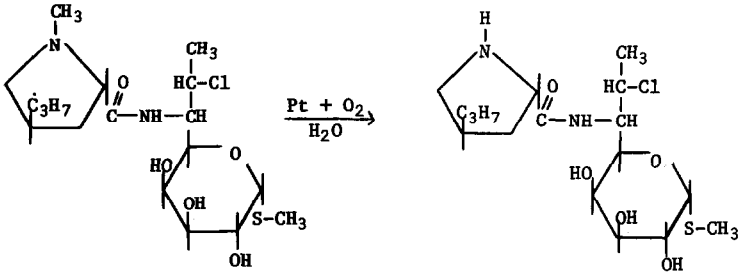
Compound	R_1	R_2	R_3	R_4
1	CH_3	HO	H	CH_3
2	CH_3	H	Cl	CH_3
3	H	HO	H	CH_3
4	H	H	Cl	CH_3
5	CH_3	HO	H	C_2H_5
6	CH_3	H	Br	CH_3
7	H	HO	H	C_2H_5
8*	H	H	Br	CH_3
9	C_2H_5	HO	H	CH_3
10	$n\text{-}C_4H_9$	HO	H	CH_3

lincolnensis var. *lincolnensis* in a modified fermentation medium. Other 1'-demethyl analogs were prepared semisynthetically by coupling a carbobenzoxy protected aminoacid with the appropriate sugar amine followed by catalytic hydrogenolysis of the carbobenzoxy group.[4] Clindamycin (2) was also converted to 1'-demethylclindamycin (4) in about 10% yield by microbial N-demethylation.[5] We now describe a novel route to the 1'-demethyllincomycins *via* oxidative N-dealkylation of lincomycin and selected analogs.

Fifty grams of clindamycin hydrochloride (2) was dissolved in 800 ml of water and stirred vigorously at 25° with 2-3 times its weight of pre-reduced platinum catalyst while air or oxygen was bubled into the reaction mixture for several days. The reaction

*This compound prepared by R. J. Reid using the procedure described here.

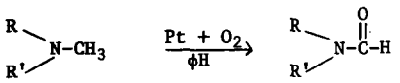
mixture was filtered, the filtrate lyophilized, and the residue crystallized from ethanol to give a 52% yield of 1'-demethyl-clindamycin (4) hydrochloride. Similar results were obtained using the free base in a mixed solvent system such as dioxane-water.



2 ·HCl 4 ·HCl

Further investigation revealed that lincomycin (1), 1-demethylthio-1-α-ethylthio-lincomycin (5) and 7(S)-bromo-7-deoxylincomycin (6) could be N-demethylated in a similar manner giving yields of 35, 51 and 13% respectively of 3, 7 and 8. The yield in the latter case was reduced due to hydrolysis of the C-7 substituent to produce 1, which was not isolated but was identified by thin layer chromatographic analysis. N-Dealkylation in the lincomycin series is not restricted to an N-methyl substituent since 1'-demethyl-1'-ethyllincomycin (9) and 1'-demethyl-1'-n-butyllincomycin (10) were converted to 3 in 30% and 50% yields.

A recent reference describes the oxidation of N-methyl tertiary amines to N-formyl secondary amines by stirring a solution of the amine in a non-polar solvent such as benzene in the presence of oxygen and platinum catalyst.[6] No reaction was observed after 72 hours



when these conditions were applied to clindamycin (2). The reaction was monitored by thin layer chromatography on silica gel. This behavior is in contrast to that observed when an aqueous solvent system is used. In the latter case the appearance of N-dealkylated product is evident by tlc within an hour of the start of the reaction.

The method of N-dealkylation described here provides a convenient synthetic route for the preparation of 1'-demethyllincomycins and a potential means of N-dealkylating other tertiary amines.

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Acceptable elemental analyses and nmr spectra were obtained for the compounds described.

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