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# A CONVENIENT METHOD FOR THE PREPARATION OF THE ACYLATED MACROLIDE ANTIBIOTIC MIDECAMYCIN USING MOLECULAR SIEVES AND ACYLCHLORIDE

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The attempted direct acylation with acylchloride of an unreactive tertiary hydroxyl group at C-3" in midecamycin in the presence of molecular sieves gave the corresponding 3"-acyl derivative under mild conditions without known 4"→3" acyl shift.

Midecamycin (1),[1,2] a fermentation product of *Streptomyces mycarofacience*, is a clinically useful 16-membered macrolide antibiotic, from which many derivatives have been synthesized.[3-5] Improvements in natural 16-membered macrolide antibiotics by acylation have been continually attempted and various acyl derivatives with better pharmaceutical properties, such as blood concentration level and taste, have been prepared to date.[6] Of the several hydroxyl groups in 16-membered macrolides, tertiary alcohol at C-3" is far less reactive than the secondary alcohols, and hence 9,3"-diacetylmidecamycin (2) was previously synthesized from the 4"-acetyl derivative of 1 by 4"→3" acetyl migration,[5] followed by the selective removal of the 2'-acetyl group in aqueous methanol utilizing the intramolecular basic catalyst at C-3".

Our investigation to prepare 9,3"-diacylmidecamycin focussed on the direct acylation of the unreactive hydroxyl group at C-3", which has not yet been achieved. As the starting material, 9,2'-diacetylmidecamycin was used which can be quantitavely prepared from the treatment of 1 with acetic anhydride in pyridine.

In the course of the investigation, 1-methyl-2-chloropyridinium iodide [7] with acetic acid and bases proved effective, giving 9,2',3"-triacetylmidecamycin together with a smaller amount of 18-enolacetate (3) in a moderate yield of about 50%.

The reaction, however, required an elevated temperature and difficult procedures for isolation.

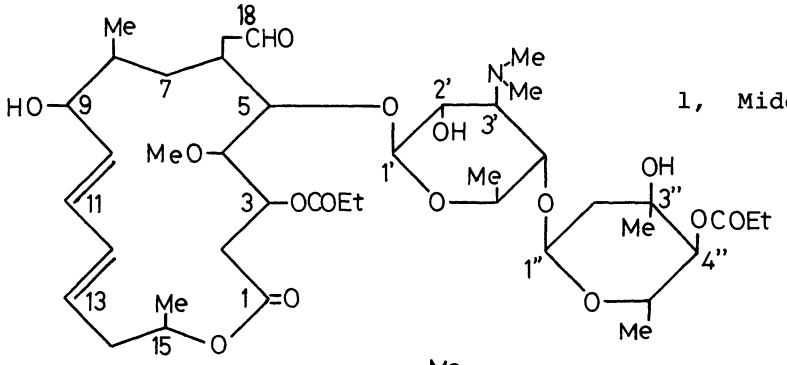
The reaction of the starting material with acylchloride in the presence of pyridine or triethylamine as acid captors caused decomposition presumably because of the basic conditions.

Considering these results, we set out to find adsorbents of hydrogen chloride.

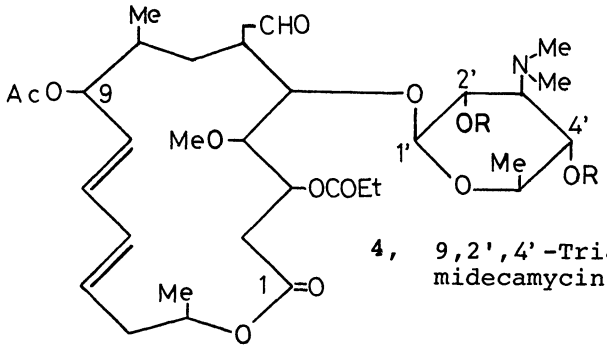
Among the examined adsorbents, which were molecular sieves, activated alumina, activated charcoal and silicic acid, the molecular sieves (type 3A and 4A) proved most useful. Several reports have referred to the ability of molecular sieves to adsorb hydrogen chloride,[8-10] and recently, the synthesis of methacrylate esters from methacryloyl chloride and various alcohols using molecular sieves as an acid captor has been reported.[11]

It was found that the best yield was given by the use of molecular sieves type 4A-30 or 4A-50 and that such solvent as ethyl acetate, dichloromethane and DMF could be used at temperatures of 40 °C to 70 °C. Besides the desired triacyl derivatives and their 18-enolacylates, triacyl demycarosylmidecamycin (4) was formed in 10 to 20% yield because of the slightly acidic conditions.

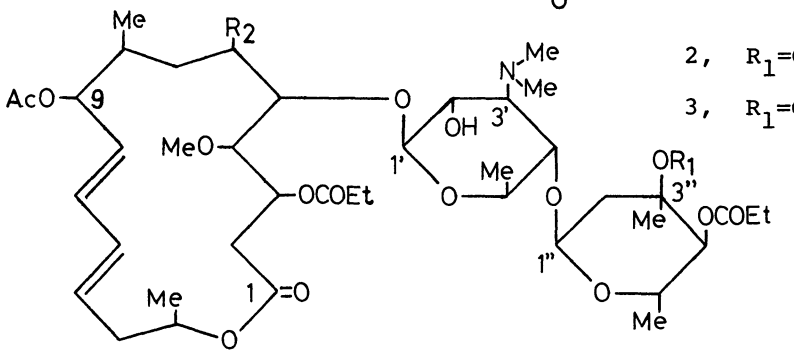
We used the typical procedure; 4A-50 type molecular sieves (21.0 g) and acetyl chloride (5.4 ml, 76 mmol) were added to an solution of 9,2'-diacetyl-midecamycin (10.8 g, 12 mmol) in ethyl acetate (24 ml) at room temperature and the resulting mixture was heated at 60 °C for 13 h. Product extraction required separation of the molecular sieves by filtration followed by successive washings with aqueous sodium hydrogencarbonate and then water. Evaporation of the solvent gave triacetyl derivative (11.0 g) as a solid. Treatment with aqueous methanol produced crude 2 (8.1 g) by partial hydrolysis of the 2'-acetyl group. Recrystallization from isopropanol gave colorless crystals of 2 (5.5 g, 51% from 9,2'-diacetyl derivative). In a similar manner, various esters of 1 were prepared in moderate yields, as shown in the table 1. The synthesized 2 and 7 showed good activities against gram positive microorganisms, while 5, 6, and 8 possessed weak activities.



1, Midecamycin



4, 9,2',4'-Triacyl-demycarosyl-midecamycin



2, $R_1$=$COCH_3$ $R_2$=$CH_2CHO$

3, $R_1$=$COCH_3$ $R_2$=$CH=CHOCOCH_3$

Table 1

The preparation of 9-acetyl-3"-acylmidecamycin

| | | Acyl group ($R_1$) | Yield (%) |
|---|---|---|---|
| Compound | 2 | $COCH_3$ | 51 |
| | 5 | $COC_2H_5$ | 38 |
| | 6 | $CO(CH_2)_2CH_3$ | 32 |
| | 7 | $COCH_2C_6H_5$ | 30 |
| | 8 | $COCH=CHC_6H_5$ (trans) | 28 |

## References

1) T. Niida, T. Tsuruoka, N. Ezaki, T. Shomura, E. Akita, and S. Inoue, J. Antibiotics, 24, 319 (1971).

2) T. Tsuruoka, T. Shomura, N. Ezaki, H. Watanabe, E. Akita, S. Inoue, and T. Niida, J. Antibiotics, 24, 452 (1971).

3) S. Inoue, S. Omoto, T. Niida, and B. Nomiya, Japanese Patent, 73 99189 (1973); Chem. Abstr., 80, 96320e (1974). Japanese Patent, 73 99188 (1973); Chem. Abstr., 80, 83547j (1974).

4) S. Omoto, S. Inoue, and T. Niida, Japanese Patent, 73 13380 (1973); Chem. Abstr., 78, 8477ly (1972).

5) S. Omoto, K. Iwamatsu, S. Inoue, and T. Niida, J. Antibiotics, 29, 536 (1976).

6) S. Omura and A. Nakagawa, J. Antibiotics, 28, 401 (1975).

7) K. Saigo, M. Usui, K. Kikuchi, E. Shimada, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 50, 1863 (1977).

8) L. M. Weinstock, S. Karady, F. E. Roberts, A. M. Hoinowski, G. S. Brenner, T. B. K. Lee, W. C. Lumma, and M. Sletzinger, Tetrahedron Lett., 3979 (1975).

9) Y. Miyake and Y. Yoshiura, Japanese Patent, 73 26683 (1973); Chem. Abstr., 79, 1802ly (1973).

10) L. B. Townsend, R. A. Earl, and S. J. Manning, U. S. Patent 3960864 (1976); Chem. Abstr., 84, 59575d (1976).

11) A. R. Banks, R. F. Fibiger, and T. Jones, J. Org. Chem., 42, 3965 (1977).

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