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C9-IMINO AND C10-AMINO DERIVATIVES OF ASCOMYCIN (21-ETHYL-FK 506)

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Abstract: Treatment of Ascomycin (21-ethyl-FK 506) with ammonia in alcoholic solution yields C9-imine 5 and C10-amine 6, whereas methylamine gives only C9-methylimine 10.

To improve the pharmacological qualities of the immunosuppressant FK 506[1] (1) chemical derivatization of the natural product or of the related macrolides Ascomycin[2] (2) and Rapamycin[3] is persued worldwide. We report on a simple one step conversion of 2 into derivatives with C9-imine or C10-amine functionalities[4] without the use of protection/deprotection protocols. Characteristics of their NMR spectra are briefly discussed.

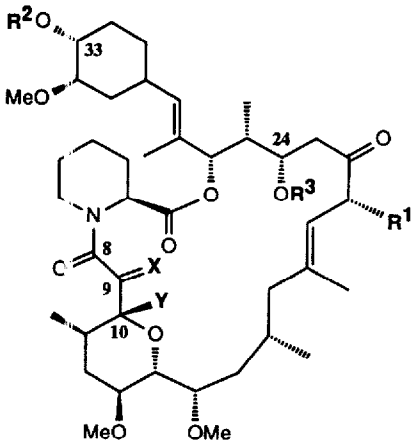
Treatment of 2 with ammonia: Excess ammonia in acetonitrile or toluene for 16 h at room temperature left 2 unchanged. Using 2M NH_3/MeOH solution as solvent two products were isolated after 1 h by chromatography in 25% (5) and 59% (6) yield. The structures were determined by ^1H and ^{13}C NMR:[5] the minor product was elucidated to be C9=NH-Ascomycin (5) and the more polar fraction to be C10-NH_2-Ascomycin (6).

The NMR spectra ($CDCl_3$) of 5, its 33-OTBDMS derivative[6] 7, 6 and its 24,33-bis-OTBMS derivative[6] 9 showed mainly two sets of signals (ratio: 4/3 for 5, 3/2 for 6, 3/2 for 7 and 2/1 for 9). Although not proven unequivocally, the following results strongly suggest that this is due to the presence of amide rotamers: 1) In $CDCl_3$ solution FK 506, Ascomycin and their 24,33-bis-OTBDMS derivatives show the presence of both possible rotamers and only one of the two possible isomers of the hemi-acetal function; 2) Monosilylation of 5 and bissilylation of 5 or 6 yielded in each case one single product: 7, 8, 9; 3) The spectra of 24,33-bissilylated imine[6] 8 in $CDCl_3$ show only one set of signals, which can be assigned to the cis form of the amide; 4) At 373° K (in $Cl_2CDCDCl_2$) the peaks of both components of 7 coincide to one set of signals (experiment not possible for 6 and 9, due to thermal instability); 5) The signals for C2 and C6 of 5, 6, 7 and 9 in the ^{13}C NMR spectra appear at ppm-values very typical for the E/Z rotameric isomers of N-acylpipecolinic derivatives.

Treatment of 2 with methylamine/methanol: In contrast to the reaction with ammonia the product mixture was much more complex containing several polar by-products. The only product corresponding to derivatives 5 and 6 was C9-N-methylimine[5] 10 (15% yield).

Presumably by the stronger base methylamine, retro-aldol reaction[1] and other base induced reaction pathways had become more dominant. This was confirmed by isolating aldehyde[1,8] **12** from the reaction mixture starting with **2** and by the increased yield (39%) of isolated bissilylated methylimine **11** after treatment of **4** with methylamine under identical conditions. According to ^{1}H and ^{13}C NMR studies **10** and **11** mainly exist in one rotameric form (cis amide) in $CDCl_3$ solution.

Similar results were obtained using ethanolic solutions of ammonia or methylamine.



1...R^1= allyl, R^2=R^3= H, X = O, Y = OH
2...R^1= ethyl, R^2=R^3= H, X = O, Y = OH
3...R^1= ethyl, R^2= TBDMS, R^3= H, X = O, Y = OH
4...R^1= ethyl, R^2=R^3= TBDMS, X = O, Y = OH
5...R^1= ethyl, R^2=R^3= H, X = NH, Y = OH
6...R^1= ethyl, R^2=R^3= H, X = O, Y = NH_2
7...R^1= ethyl, R^2= TBDMS, R^3= H, X = NH, Y = OH
8...R^1= ethyl, R^2=R^3= TBDMS, X = NH, Y = OH
9...R^1= ethyl, R^2=R^3= TBDMS, X = O, Y = NH_2
10...R^1= ethyl, R^2=R^3= H, X = NMe, Y = OH
11...R^1= ethyl, R^2=R^3= TBDMS, X = NMe, Y = OH

Derivatives **5** and **6** show high immunosuppressive activity in vitro , comparable to that of the parent compound Ascomycin, whereas introduction of the C9-methylimino function (**10**) causes a decrease in efficacy. Due to the modified tricarbonyl reactivity, the described compounds represent valuable intermediates for further selective functional group conversions.

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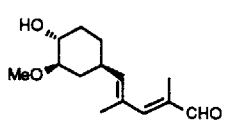
3. Vezina, C.; Kudelski, A.; Sehgal, S.N., J. Antibiotics **1975**, 28, 721-726.
4. Compare: Donald, D.K.; Cooper, M.E.; Furber, M.; Wells, E.; Hutchinson, R.; Black, F.M., Tetrahedron Lett. **1991**, 32(10), 1375-1378.
5. Typical ^{13}C NMR signals[ppm] in $CDCl_3$; **5** (2 rotamers): 175.6/170.8 (C9), 96.4/95.5 (C10); **6** (2 rotamers): 198/196 (C9), 88.6/88.5 (C10); **10**: 164.4 (C9), 95.5 (C10).
6. To confirm the determined structures, **7**, **8** and **9** were synthesized not only by mono-/bissilylation of **5** and **6**, respectively, but also by treatment of **3** or **4** with ammonia.
7. Mierke, D.F.; Schmieder, P.; Karuso, P.; Kessler, H., Helv. Chim. Acta **1991**, 74, 1027-1047.
8. 

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