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OXIDATION OF AMINO ACID. PART V*. A NOVEL SYNTHESIS OF N^6-ACETYL-N^6-HYDROXYLYSINE FROM LYSINE

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Abstract: N^6-Acetyl-N^6-L-hydroxylysine was synthesized from L-lysine by oxidation of the amino group in the N^2-benzyloxycarbonyl-L-lysine tert-butyl ester with benzoyl peroxide and subsequent acetylation.

Nature has taken advantage of the ω-amino group of ornithine and lysine to construct secondary hydroxamic acid residues in siderophores[2]. However, ω-N-hydroxylysine, found in aerobactin[3], mycobactines[4] and exochelins[5], the key to the synthesis of most of the hydroxamate-containing siderophores, has received very little synthetic attention. Nielands[6] was the first to prepare the noncrystalline dihydrochloride and the crystalline mono-2-nitro-1,3-indandione salts of N^6-hydroxylysine. Attempts to synthesize N-hydroxylysine through the N-oxide were unsuccessful[7]. Lately, N^6-acetyl-N^6-hydroxylysine was obtained by alkylation of the hydroxamate with alcohol in the presence of triphenylphosphine/diethyl azodicarboxylate (DEAD)[8].

Continuing our research on the oxidation of the amino acid amino group[9], in our previous work[1] we reported the optimum conditions of the oxidation of the amino group in ω-monoamino acid esters with benzoyl peroxide, under conditions similar to those described by Zinner[10] for the oxidation of primary amines.

Now we present the synthesis of the N^6-acetyl-N^6-hydroxylysine derivative by oxidation with benzoyl peroxide. N^2-Benzyloxycarbonyl-L-lysine[11] (1 eqv.) was treated with tert-butyl acetate (13.5 ml) in the presence of perchloric acid (1.1 eqv.) giving the ester 1 (yield 58%)[12].

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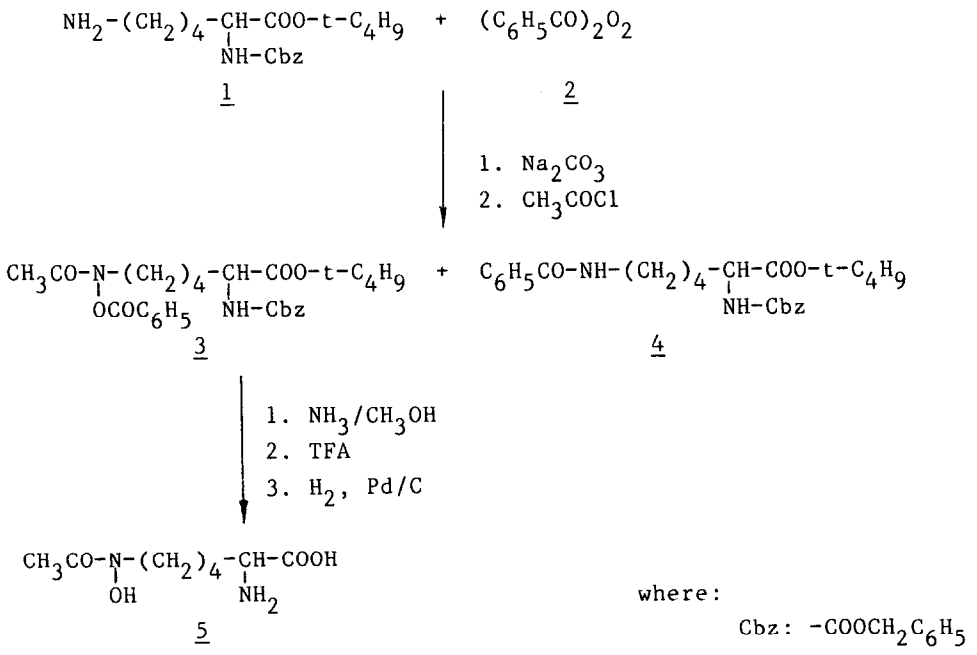
* for part IV see[1]



where:

Cbz: $-COOCH_2C_6H_5$

Ester 1 (1 eqv.) in CH_2Cl_2 (5 ml) was oxidized with benzoyl peroxide 2 (1 eqv.) in the presence of sodium carbonate (5 eqv.). The products were not isolated but acetylated in situ with acetyl chloride under Schotten-Baumann conditions. The separation of amide 4 and the hydroxamic acid derivative 3 was carried out applying chromatography on silica gel (Merck <200 mesh; benzene as eluent). The yield of product 3 was 58% and the undesired amide 4 - 27%[13].

The ester 3 (1 eqv.) was easily transformed into N^6-acetyl-N^2-benzoxy-carbonyl-N^6-hydroxylysine tert-butyl ester with 10% ammonia in methanol (3 ml) (yield 90%)[14]. Each of the other two protective groups i.e. the tert-butyl ester and the benzyloxycarbonyl group may selectively be removed applying acidolysis with trifluoroacetic acid or hydrogenolysis with H_2 in the presence of Pd/C[15], giving useful synthons for siderophore synthesis.

N^6-Acetyl-N^6-L-hydroxylysine 5[16] was obtained as the result of subsequent acidolysis with trifluoroacetic acid (20 min., ambient temp.) and hydrogenolysis (5% Pd/C, 20 min., in ethanol). Product 5 was purified with Zerolit 225 [H^+], 100-200 mesh.

Acetyl-N-hydroxyornithine was synthesized by the same route. The full results will be published shortly.

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12. Compd. 1x$CH_3C_6H_4SO_3H$ (white crystals): mp. 179-81° from ethyl acetate/ether; calc. for $C_{25}H_{36}N_2O_7S$ C 59.04, H 7.13, N 5.51%; found C 59.21, H 7.22, N 5.79%; $[\alpha]_D^{20}=-4^o$ (c 3, CH_3OH); ^{1}H-NMR ($CDCl_3$): 1.3-1.9 (m, 6H, $-CH_2-$); 1.35 (s, 9H, t-C_4H_9); 2.9 (m, 2H, $-CH_2\overset{+}{N}H_3$); 4.05 (m, 1H, >CHNH-); 5.0 (s, 2H, $-CH_2C_6H_5$); 5.7 (d, 1H, -NH-); 7.2 (s, 5H, C_6H_5-); 7.9 (m, 3H, $\overset{+}{N}H_3-$).

13. Compd. 3 (oil): calc. for $C_{27}H_{34}N_2O_7$ C 65.04, H 6.87, N 5.62%; found C 64.91, H 7.06, N 5.32%; $[\alpha]_D^{20}=+4^o$ (c 2.7 $CHCl_3$); R_f (S1) 0.5; MS.EI m/e (%): 91 (98) [C_7H_7], 105 (100) [COC_6H_5], 204 (71) [Ac/OH/Lys], 320 (18.7) [M-(t-C_4H_9+$CO_2C_6H_5$) and M-(CH_3CO+$CO_2C_7H_7$)], 442 (13) [M-C_4H_8]; ^{1}H-NMR (CCl_4): 1.1-1.8 (m, 6H, $-CH_2-$); 1.4 (s, 9H, t-C_4H_9); 1.9 (s, 3H, CH_3CO-); 3.7 (t, 2H, $-CH_2N<$); 4-4.25 (m, 1H, >CHNH-); 5 (s, 2H, $-CH_2C_6H_5$), 5.5 (d, 1H, -NH-); 7.25 (s, 5H, $C_6H_5CH_2-$); 7.25-7.7 (m, 3H, C_6H_5CO-); 7.9-8.2 (m, 2H, C_6H_5CO-);

Compd. 4 (oil): calc. for $C_{25}H_{32}N_2O_5$ C 68.16, H 7.32, N 6.36%; found C 68.07, H 7.43, N 6.26%; R_f (S1) 0.3; ^{1}H-NMR ($CDCl_3$): 1.2-1.9 (m, 6H, $-CH_2-$); 1.4 (s, 9H, t-C_4H_9-); 3.4 (q, 2H, $-C\underline{H}_2NH-$); 4-4.4 (m, 1H, $-C\underline{H}NH-$); 5.15 (s, 2H, $-C\underline{H}_2C_6H_5$); 5.53 (d, 1H, -NH-); 6.6 (m, 1H,-NH-); 7.25 (s, 5H, $C_6\underline{H}_5CH_2-$); 7.2-7.55 (m, 3H, C_6H_5CO-); 7.7-7.9 (m, 2H, C_6H_5CO-).

14. N^6-Acetyl-N^2-benzyloxycarbonyl-N^6-L-hydroxylysine tert-butyl ester (oil): calc. for $C_{20}H_{30}N_2O_6$ C 60.89, H 7.66, N 7.10%; found C 60.71, H 7.76, N 7.05%; $[\alpha]_D^{20}=+10^o$ (c 2.4 $CHCl_3$); R_f (S1) 0.2; ^{1}H-NMR ($CDCl_3$): 1.2-1.9 (m, 6H, $-CH_2-$); 1.4 (s, 9H, t-C_4H_9-); 2 (s, 3H, CH_3CO-); 3.5 (t, 2H, $-CH_2N<$); 4-4.35 (m, 1H, $>C\underline{H}NH-$); 5.06 (s, 2H, $-C\underline{H}_2C_6H_5$); 5.56 (d, 1H, -NH-); 7.33 (s, 5H, C_6H_5-);

15. N^6-Acetyl-N^2-benzyloxycarbonyl-N^6-L-hydroxylysine (yellow solid): calc. for $C_{16}H_{22}N_2O_6$ - N 8.28%; found N 8.35%; R_f (S2) 0.64; ^{1}H-NMR ($CDCl_3$): 1.1-2 (m, 6H, $-CH_2-$); 2.03 (s, 3H, CH_3CO-); 3.5 (m, 2H, $-CH_2N<$); 4.23 (m, 1H, $>C\underline{H}NH-$); 5.0 (s, 2H, $-C\underline{H}_2C_6H_5$); 5.95 (m, 1H, -NH-); 7.2 (s, 6H, C_6H_5-, >NOH);

N^6-Acetyl-N^6-L-hydroxylysine tert-butyl ester (oil): calc. for $C_{12}H_{24}N_2O_4$ N 10.76%; found N 11.29%; R_f (S2) 0.56; ^{1}H-NMR ($CDCl_3$): 1.3-1.9 (m, 6H, $-CH_2-$); 1.4 (s, 9H, t-C_4H_9-); 2.1 (s, 3H, CH_3CO-); 3.6 (m, 3H, $>C\underline{H}NH-$, $CH_2N<$); 6.35 (m, 3H, -OH, NH_2);

16. N^6-Acetyl-N^6-L-hydroxylysine 5 (white crystals): mp. 209-10°C from ethanol aq.; calc. for $C_8H_{16}N_2O_4$ C 47.05, H 7.90, N 13.72%; found C 46.88, H 8.00, N 13.75%; $[\alpha]_D^{20}=+2^o$ (c 5.6, H_2O); R_f (S2) 0.31; ^{1}H-NMR (D_2O): 1.2-2 (br m, 6H, $-CH_2-$); 2 (s, 3H, CH_3CO-); 3.6 (m, 3H, $-CH_2N<$, $>C\underline{H}NH_2$).
Lit. data[8] for N^6-acetyl-N^6-DL-hydroxylysine: mp. 236-7°C, ^{1}H-NMR (D_2O): 1.1-2.1 (br m, 6H); 2.0 (s, 3H); 3.5 (m, 3H).
S1 - benzene; ethyl acetate; ethanol / 8:2:0.5
S2 - n-butanol; water; acetic acid / 4:1:1

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