SYNTHESIS OF NICOTIANAMINE AND A RELATED COMPOUND, DERIVATIVES OF AZETIDINE-2-CARBOXYLIC ACID[†]

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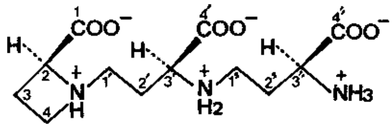
Abstract — The synthesis of nicotianamine (1) and a related compound (2) — amino acid derivatives having the azetidine ring — was achieved by reductive coupling of L-aspartic-β-semialdehyde derivatives with L-azetidine-2-carboxylic acid methyl ester.

Nicotianamine (1) is a unique amino acid containing the azetidine-2-carboxylic acid moiety, first isolated from the leaves of Nicotiana tabacum.[1] Its structure was elucidated as 2(S), 3'(S),3''(S)-N-[N-(3-amino-3-carboxypropyl)-3-amino-3-carboxypropyl]-azetidine-2-carboxylic acid by spectral analysis and by the chemical transformation from L-azetidine-2-carboxylic acid (A2C) (13).[2] Nicotianamine (1) has also been found in many species of Solanaceae and some other plants.[3] In spite of the wide distribution, the biological significance of this compound is still uncertain.

On the other hand, several amino acid derivatives related to nicotianamine (1) such as mugineic acid (3)[4,5] and avenic acid A (4)[6] have been isolated from the excreta of the roots of oats cultured under iron deficient conditions. These acidic amino acids possess an iron chelating activity and play a role in iron uptake and transport.[7] During the course of our attempts to isolate such chelating amino acid derivatives, avenic acid B (5) was isolated from the root extract



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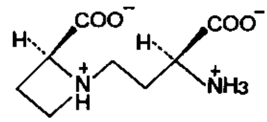

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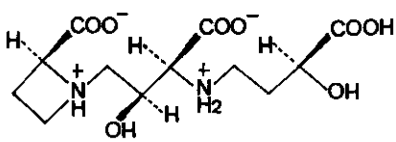

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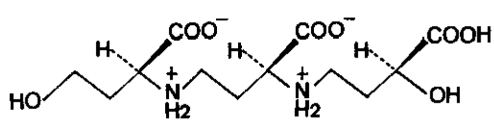

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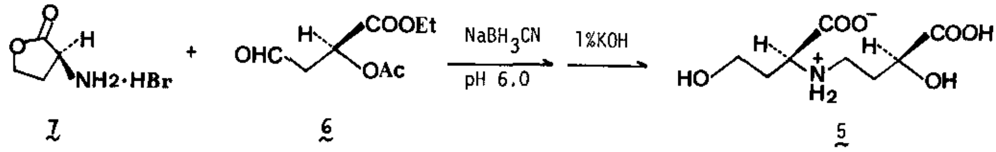
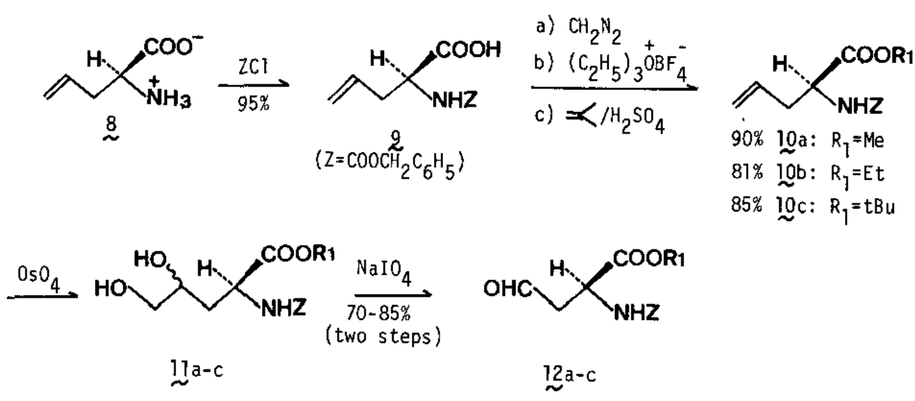
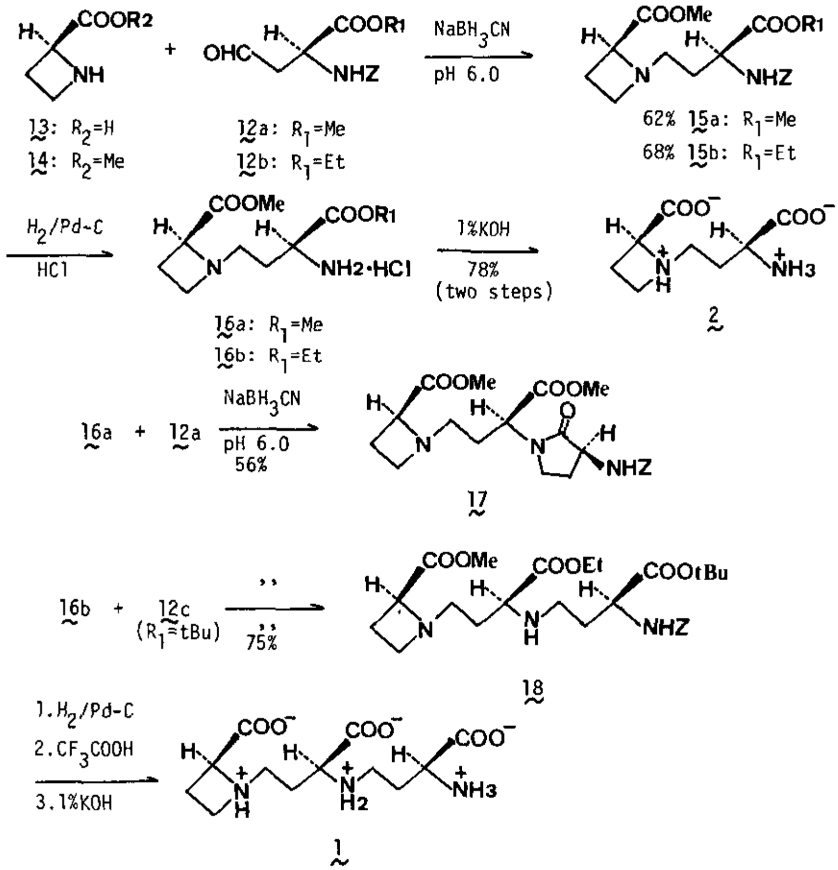


of Avena sativa. In our last paper,[8] we described the synthesis of this compound via reductive coupling of L-malic semi-aldehyde derivative 6 with L-homoserine lactone 7 by using $NaBH_3CN$, a selective reducing agent. It is thought that other chelating amino acids and related compounds, in which two or three molecules are connected through a C-N bond, can be synthesized as optically active forms by the same method. In the present communication, we describe the synthesis of nicotianamine (1) and A2C dimer (2), 2(S),3'(S)-N-(3-amino-3-carboxypropyl)-azetidine-2-carboxylic acid isolated from the seeds of Fagus silvatica L. along with nicotianamine (1).[2]

The synthesis of 2 was achieved through reductive coupling of L-aspartic-β-semialdehyde derivative 12a to A2C methyl ester 14 by using $NaBH_3CN$ after deprotection and, in the case of 1 two moles of aldehydes (12b and 12c) were combined stepwise with 14.[9] Since L-aspartic-β-semialdehyde is a important biogenetic precursor of L-homoserine and L-methionine, this compound might be a unit in the biosynthesis of nicotianamine (1), iron chelating amino acids and other C-4 amino acid derivatives. The requisite aldehydes 12a-c were synthesized in a fair yield from L-allylglycine 8 according to the method of Neuberger[10] with a modification. Treatment of L-allylglycine 8 with carbobenzoxy chloride, followed by esterification with a) diazomethane b) Meerwein reagent and c) isobutylene gave corresponding esters 10a-c. Osmium tetraoxide oxidation of the esters 10a-c afforded diols 11a-c, which were oxidized with sodium metaperiodate yielding corresponding aldehydes 12a-c: $[\alpha]_D$ +29.9°, +19.7° and +15.1° ($CHCl_3$), respectively. The signals due to the aldehyde protons were observed at 9.68-9.73 ppm in the pmr spectra of the aldehydes 12a-c.



In preference to the synthesis, an authentic sample of nicotianamine (1) was isolated from young leaves of Lycium chinence.[3] The spectral data of isolated 1 (mp 243°(decom.), $[\alpha]_D$ -48.0° (c=0.2, H_2O)) were shown to be identical with those in the literature.[1,2] Reaction of the aldehyde 12a and A2C methylester 14 with $NaBH_3CN$ at pH 6.0 afforded 15a in a 62% yield: $[\alpha]_D$ -60.5° (c=0.5, $CHCl_3$); ms, m/e 364.1658 (calc'd for $C_{18}H_{24}N_2O_6$, 364.1635); ir ($CHCl_3$) 1720, 1495, 1225, 1045 cm^{-1}; pmr ($CDCl_3$) δ 7.33 (5H, s, $-C_6\underline{H}_5$), 6.47 (1H, d, J=8, $-N\underline{H}$), 5.12 (2H, s, $OC\underline{H}_2-C_6H_5$), 4.38 (1H, m, $C_{(3')}\underline{H}$), 3.69, 3.72 (each 3H, s, $-OC\underline{H}_3$), 3.60 (1H, t, J=8, $C_{(2)}\underline{H}$), 3.39 (1H, m, $C_{(4)}\underline{H}a$), 2.80 (1H, m, $C_{(4)}\underline{H}b$), 2.4-2.9 (2H, m, $C_{(1')}\underline{H}_2$), 2.1-2.4 (2H, m, $C_{(3)}\underline{H}_2$), 1.6-2.0 (2H, m, $C_{(2')}\underline{H}_2$). In the case of 12b and 14, 15b was obtained in a 68% yield: $[\alpha]_D$ -78.0° (c=0.1, $CHCl_3$). Deprotection of 15a: 1. H_2/10% palladium carbon, 2. 1% methanolic potassium hydroxide, followed by chromatographic purification on a Dowex 50W column afforded the compound 2: $[\alpha]_D$ -81.8° (c= 0.06, H_2O). The paper chromatography Rf value, $[\alpha]_D$ and the pmr spectrum of the synthetic specimen of 2 were shown to be identical with those of the natural one in the literature.[2]



Reaction of the aldehyde 12a with 16a, the decarbobenzoxylation product of 15a in the presence of $NaBH_3CN$ at pH 6.0 gave a lactam 17: $[\alpha]_D$ -45.3° (c=0.2, $CHCl_3$), in a 56% yield. The expected 18 was obtained by reductive condensation of the aldehyde 12c to 16b in a 75% yield: $[\alpha]_D$ -35.4° (c= 0.1, $CHCl_3$); ms, m/e 535.2909 (calc'd for $C_{27}H_{41}N_3O_8$, 535.2893); ir ($CHCl_3$) 1720, 1500, 1367, 1230, 1150 cm^{-1}; pmr ($CDCl_3$) δ 7.32 (5H, s, $-C_6\underline{H}_5$), 6.19 (1H, d, J=8, $-N\underline{H}$), 5.08 (2H, s, $O-C\underline{H}_2-C_6H_5$), 4.15 (2H, q, J=7, $O-C\underline{H}_2CH_3$), 4.2-4.3 (1H, m, $C_{(3'')}\underline{H}$), 3.66 (3H, s, $-OC\underline{H}_3$), 3.2-3.7 (3H, m, $C_{(2)}\underline{H}$, $C_{(3')}\underline{H}$, $C_{(4)}\underline{H}a$), 2.0-2.9 (7H, m, $C_{(4)}\underline{H}b$, $C_{(1')}\underline{H}_2$, $C_{(1'')}\underline{H}_2$, $C_{(3)}\underline{H}_2$), 1.25 (3H, t, J=7, $-CH_2C\underline{H}_3$), 1.45 (9H, s, $-C(C\underline{H}_3)_3$), 1.5-2.0 (4H, m, $C_{(2')}\underline{H}_2$, $C_{(2'')}\underline{H}_2$). Deprotection of 18: 1. H_2/10% palladium carbon, 2. trifluoroacetic acid, 3. 1% potassium hydroxide, followed by chromatographic purification on a Dowex 50W column furnished the compound 1: mp 247° (decom.), $[\alpha]_D$ -45.8° (c=0.1, H_2O). The specimen of synthetic 1 was shown to be identical with natural nicotianamine in all respects including the paper chromatography Rf value, Rt on HPLC and pmr spectrum. Further the synthetic 1 showed no melting point depression in the mixed mp test with natural nicotianamine.

As mentioned above, the optically active nicotianamine (1) and A2C dimer (2) were synthesized by reductive coupling of A2C methyl ester 14 and aspartic-β-semialdehyde derivatives 12a-c and, the synthesis of the chelating amino acid derivatives and related compounds by the same method is now under investigation.

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