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STRUCTURE AND SYNTHESIS OF LENTYSINE, A NEW HYPOCHOLESTEROLEMIC SUBSTANCE

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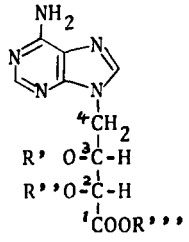
T.Kaneda and others mentioned that methanol extracts of Lentinus edodes Sing. (SHIITAKE, a species of mushroom) have high hypocholesterolemic activity[1]. Recently, they have isolated an active substance and assumed its structure as a kind of peptide[2].

T.Rokujo and others have reported an active substance, named lentysine by them, from SHIITAKE[3].

In this communication, we wish to report the structure and synthesis of lentysine.

Lentysine (I) was obtained as colorless needles, $C_9H_{11}O_4N_5$[4], m.p. 279° (dec.), $[\alpha]_D$ +50° (0.1 N NaOH) and +16° (N HCl). The uv spectra, $\lambda_{max}^{H_2O}$ 261 mμ (ε , 14,300), $\lambda_{max}^{0.5\ N\ HCl}$ 260 mμ (ε , 14,000) and $\lambda_{max}^{0.5\ N\ NaOH}$ 261 mμ (ε , 14,300), suggest the presence of 9-substituted adenine nucleous, which is also supported by signals at τ 1.85 (1H, siglet) and 1.99 (1H, singlet) in the nmr spectrum[5]. The ir spectrum reveals the presence of hydroxy groups (3500~2200 cm^{-1}) and carboxylic acid (1698 cm^{-1}).

Treatment of lentysine with diazomethane gave methyl ester (II), $C_{10}H_{13}O_4N_5$, m.p. 231° (dec.), mol. wt. 276 (mass spectrum). On acetylation with acetic



I : R'=R''=R'''=H

II : R'=R''=H, R'''=CH_3

III : R'=R''=$COCH_3$, R'''=CH_3

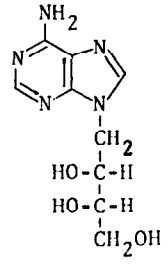
IV : R' , R'' = $>C<^{CH_3}_{CH_3}$, R'''=CH_3

anhydride-pyridine at room temperature, II gave diacetate (III), $C_{14}H_{18}O_6N_5$, m.p. 225° (dec.), mol. wt. 351 (mass spectrum).

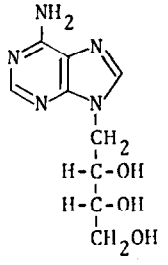
The nmr spectrum of III shows signals at τ 4.45 (1H, broad quartet, J=5 ~6 Hz), 4.87 (1H, doublet, J=5 Hz) and 5.50 (2H, doublet, J=6 Hz). The signals at τ 4.45 and 4.87 are corresponding to C_3- and C_2- protons adjacent together and τ 5.50 signal is assignable to C_4- methylene protons neighboring to the C_3- proton. From these data, lentysine should be represented by formula (I).

The stereochemistry of the vicinal glycol is assumed to be erythro configuration by analogy with the nucleosides. This assumption is supported by the nmr spectrum of acetonide (IV), $C_{13}H_{17}O_4N_5$, m.p. 181°, which was obtained by treatment of II with acetone-phosphorus oxychloride. The C_4- methylene signal of IV, appearing at τ 5.6~6.1 in II, has shifted downfield to τ 5.08. This high degree of deshielding suggests that the C_4- methylene group is oriented cis with respect to the carboxyl group (erythro configuration).

Evidence for the erythro configuration was derived from triol (V), $C_9H_{13}O_3N_5$, m.p. 219~20°, $[\alpha]_D$ +30° (N HCl), obtained by reduction of II with $NaBH_4$ in isopropanol. This V was found to be the mirror image of triol (VI)[6] by comparison with their physical properties.



V

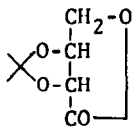


VI

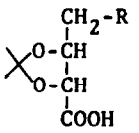
Furthermore, the absolute configuration of lentysine (I) was determined to be D-erythro form (2-(R), 3-(R) configuration) from the above fact.

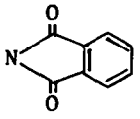
The structure and the stereochemistry of lentysine (I) were confirmed synthetically. Reaction of 2,3 -O-isopropylidene-D-erythronolactone (VII) with potassium phthalide gave acid (VIII), $C_{15}H_{15}O_6N$, m.p. 196° (dec.), $[\alpha]_D$ +84° (0.1 N NaOH) in 80 % yield. Partial hydrolysis of VIII with hydrazine hydrate

yielded amino acid (IX)[7], $C_7H_{13}O_4N \cdot H_2O$, m.p. 189° (dec.), $[\alpha]_D$ +85° (60% acetone).

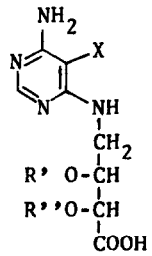


VII



VIII : R= 

IX : R= NH_2



X : R', R'' = $=C(CH_3)_2$, X= NO_2

XI : R', R'' = $=C(CH_3)_2$, X= NH_2

XIII : R'=R''=H, X= NHCHO

Condensation of IX with 4-amino-6-chloro-5-nitropyridine gave nitro acid (X), $C_{11}H_{15}O_6N_5$, m.p. 228° (dec.), $[\alpha]_D$ +100° (0.1 N NaOH), $\lambda^{EtOH}_{shoulder}$ 230 mμ (ε , 17,700) and λ^{EtOH}_{max} 339 (10,100) in 94% yield. Catalytic reduction of X with Raney nickel led to amino acid (XI), $C_{11}H_{17}O_4N_5 \cdot 2H_2O$, m.p. 223° (dec.), $[\alpha]_D$ +69° (0.1 N NaOH), $\lambda^{H_2O}_{max}$ 218 mμ (ε , 26,600) and 280 (10,800) in 90% yield. This XI was treated with formic acid to yield formyl amino acid (XII), $C_{12}H_{17}O_5N_5$, m.p. 190° (dec.), $\lambda^{H_2O}_{max}$ 222 mμ (ε , 35,100) and 265 (7,100) in quantitative yield. Finally, treatment of XII with aqueous NaOH underwent cyclization to 4-(6-aminopurin-9-yl)-4-deoxy-D-erythronic acid (I), $C_9H_{11}O_4N_5$, m.p. 279° (dec.), $[\alpha]_D$ + 52° (0.1 N NaOH), +15° (N HCl) in 90% yield. This product was identical in all respects with the natural lentysine.

Further studies on lentysine and the related compounds will be reported.

References

1. T.Kaneda and S.Tokuda, J. Nutrition, 90 371 (1966).
2. T.Kaneda, N.Shibukawa, S.Tokuda and F.Tsuneda, Abstr. 23rd General Meeting of Japanese Soc. of Food and Nutrition, Kyoto (1969), p.49.
3. T.Rokujo, H.Kikuchi, A.Tensho, Y.Tsukitani, T.Takenawa and K.Yoshida, Nature in press.
4. Satisfactory elemental analysis were obtained for all compounds with formulas cited. Melting point measurements of these compounds are uncorrected.
5. All nmr spectra were measured in d6-DMSO at 60 Mz on a Varian Model A-60 spectrometer.
6. M.Ikehara and E.Ohtsuka, Chem. Pharm. Bull. (Tokyo), 11 1095 (1963). we are grateful to Prof. M.Ikehara for his kind supply of the sample.
7. IX had been synthesized through another route from VII by S.Hanessian, J. Org. Chem., 34 675 (1969).