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SYNTHESES OF D-THREO- AND L-THREO-LENTYSINE

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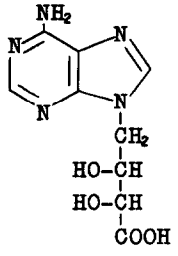
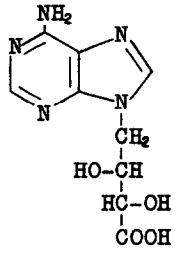
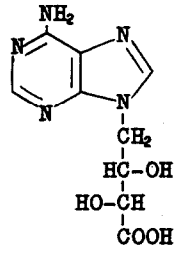
In the course of our studies on the synthesis of lentysine (I)[1,2], a high hypocholesterolemic substance isolated from Lentinus edodes Sing. (SHIITAKE), it was found that 2.3-O-isopropylidene-D-erythronolactone (IV)[3] was transformed with epimerization into methyl 2.3-O-isopropylidene-D-threonate (VI) by treatment with methoxide anion. The present communication is concerned with this epimerization and its application to the conversion of lentysine (I) to D-threo-lentysine (II). The synthesis of L-threo-lentysine (III) by an independent route was also described herein.



I



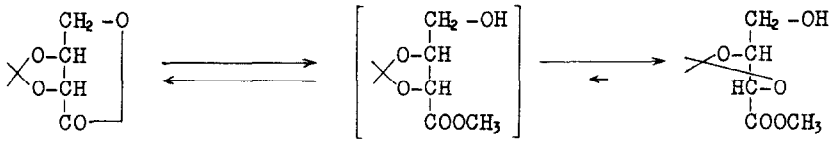
II



III

On treatment of the lactone (IV) with barium methoxide in methanol, a hydroxy methyl ester (VI), $C_8H_{14}O_5$[4], b.p. 90-3°/0.5 mm Hg, was obtained with the recovery of some starting material unchanged. The structure was assigned to be methyl 2.3-O-isopropylidene-D-threonate (VI) from the fact that, on treatment with hydrochloric acid followed by benzoylation with benzoyl chloride in pyridine, VI was converted to D-threonolactone dibenzoate (VII), $C_{18}H_{14}O_6$, m.p.

114°, $[\alpha]_D$ -185° (C_2H_5OH), whose structure was confirmed by comparison with L-threonolactone dibenzoate (VIII)[5] derived from ascorbic acid.



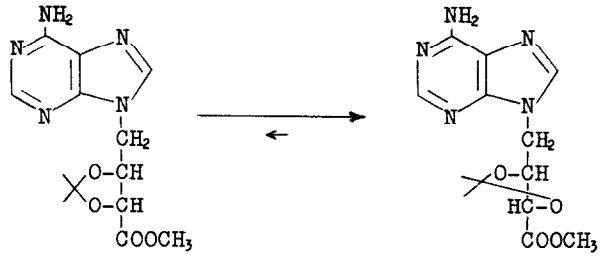
IV V VI

VII VIII

The hydroxy methyl ester (VI) could be considered as the epimerized product of methyl 2.3-O-isopropylidene-D-erythronate (V), which is expected to be initially produced from the lactone (IV). This erythro isomer (V) should be in an equilibrium with the threo one (VI) in the reaction solution, since treatment of the threo isomer (VI) with barium methoxide gave erythronolactone acetonide (IV)(the ratio of IV and VI was 1:6), the lactone formation being explained in terms of the facile lactonization of the erythro isomer (V).

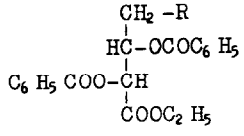
This finding prompted us to examine the conversion of lentysine (I) to D-threo-lentysine (II). When lentysine acetonide methyl ester (IX)[1] was treated with sodium methoxide, the epimerized product (X), $C_{13}H_{17}O_4N_5$, m.p. 211-2°, was obtained. Consecutive alkaline and acidic hydrolysis of X yielded D-threo-lentysine (II), $C_9H_{11}O_4N_5$, m.p. 297° (dec.), $[\alpha]_D$ +82° (0.1 N NaOH).

When X was conversely treated with sodium methoxide, a mixture of IX and X was obtained in a ratio of 1:16. This different ratio from that in the case of VI suggests that the equilibrium position may be governed by the steric factors of the 4-substituents (the adenine nucleus and the hydroxy group respectively) to the methoxycarbonyl group in the two sets of the acetonides.

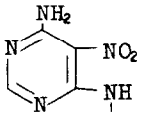


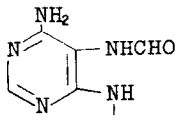
IX X

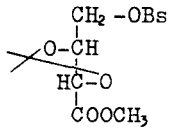
The structure of D-threo-lentysine (II) was conclusively confirmed by comparison with L-threo-lentysine (III) synthesized by an independent route as follows. L-Threonolactone dibenzoate (VIII) was treated with ethanol-hydrobromic acid to give the oily hydroxy ethyl ester (XI), which was successively converted to the tosylate (XII) by p-toluenesulfonyl chloride in pyridine. This tosylate (XII) was treated with sodium azide in dimethylsulfoxide and the resulting oily azido compound (XIII) was hydrogenated on palladium to yield the amine (XIV), $C_{20}H_{21}O_6N \cdot HCl$, m.p. 191-2° (dec.). Condensation of the amine (XIV) with 4-amino-6-chloro-5-nitropyrimidine gave the product (XV), $C_{24}H_{23}O_8N_5 \cdot HCl$, m.p. 198-200° (dec.), which was hydrogenated on palladium in formic acid. The reductive formylation product (XVI), without isolation, was cyclized with sodium hydroxide to afford L-threo-lentysine (III), $C_9H_{11}O_4N_5$, m.p. 297° (dec.), $[\alpha]_D$ -81° (0.1 N NaOH).



XI, R=OH
XII, R=OTs
XIII, R=N_3
XIV, R=NH_2

XV, R= 

XVI, R= 



XVII

D-threo-lentysine acetonide methyl ester (X) was also obtained by condensation of sodium adenide and the brosylate (XVII), $C_{14}H_{17}O_7SBr$, m.p. 70-1°, according to the method of N. J. Leonard, et al.[6] XVII was derived from the hydroxy methyl ester (VI) by treatment with p-bromobenzenesulfonyl chloride in pyridine.

References

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