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A NEW PYRIMIDINE ANALOG OF m-TYROSINE

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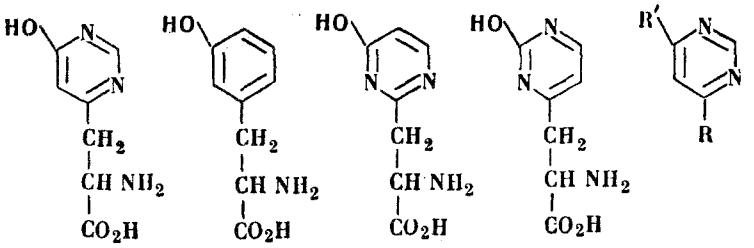
Synthesis of the hitherto unknown β-(6-hydroxypyrimidyl-4)alanine, a pyrimidine analog of m-tyrosine, is effected. It is based on conversion of ethyl β-(6-methoxypyrimidyl-4)pyrotartrate to an α-hydroxyimino derivative followed by reduction of the latter in acid medium. The synthesis of β-(6-hydroxypyrimidyl-4)alanine completes the preparation of the series of all theoretically possible pyrimidine analogs of m-tyrosine.

In connection with a study of potential antimetabolite substances participating in nuclein-protein metabolism, synthesis of β-(6-hydroxypyrimidyl-4)alanine (I) was undertaken. It is a close structural analog of m-tyrosine (Ia), and of recent years the latter has attracted the attention of researchers as it has interesting pharmacological properties [1-3], and because it is an actual precursor of the new biogenous amine leptodactyline, found in amphibians of the species Leptodactylus [4-6].



I Ia Ib Ic Id, II

Id $R=CH_2 \cdot CO \cdot CO_2C_2H_5$, $R'=OCH_3$;
II $R=CH_2 \cdot C(:N \cdot OH) \cdot CO_2C_2H_5$, $R'=OCH_3$.

The present investigation established that synthesis of the pyrimidylamino acid I, isomeric with the previously obtained pyrimidine analogs of m-tyrosine β-(4-hydroxypyrimidyl-2)alanine (Ib) [7], and β-(2-hydroxypyrimidyl-4)alanine (Ic) [8] can be successfully accomplished, starting from ethyl β-(6-methoxypyrimidyl-4)-pyrotartrate (Id) [9], which reacts smoothly with hydroxylamine to give ethyl α-oximino-β-(6-methoxypyrimidyl-4)propionate (II). The transition from the latter to amino acid I is readily effected by treatment with stannous chloride in acid medium, which simultaneously secures reduction of the ketoxime portion, and saponification of the ester group.

Constants and Yields of Amino Acid I and Ester II

Compound No.	Mp, °C	R_f in the system*			UV spectrum in 0.1 N NaOH		Electrophoretic mobility $\times 10^5$ cm$^2 \cdot V^{-1} \cdot sec^{-1}$		Yield, %
		A	B	C	λ_{max}, mμ	lg ε	pH 1.7	pH 9.0	
I	275 (Decomp.)	0.52	0.00	0.25	232 262	4.92 4.59	−1.8	+1.6	52
II	182—183	0.90	0.88	0.70	254	5.58	−12.5	+5.0	89

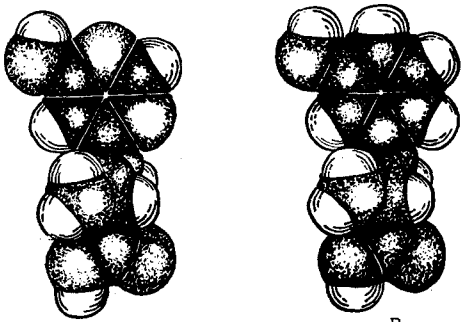
*A) n-C_4H_9OH + H_2O + CH_3COOH (4 : 5 : 1); B) n-C_4H_9OH, saturated with water; C) i-C_3H_7OH + 25% NH_3 + H_2O (14 : 1 : 5).

The new pyrimidylamino acid is a colorless crystalline compound, readily soluble in water, of limited solubility in ethanol, and practically insoluble in ether and benzene. It has amphoteric properties, exhibits a characteristic UV absorption in the near UV, and gives a positive brownish-yellow ninhydrin reaction.

Information about constants and yields of amino acid I and ester II are given in the Table.

The extent of spatial similarity between the pyrimidylamino acid I and m-tyrosine can be judged from molecular models, as shown in the figure.

Finally, it should be mentioned that synthesis of the amino acid I completes preparation of a series of all theoretically possible pyrimidine analogs of m-tyrosine (see formulas I-Ic).



Stuart-Brigleb molecular models of β-(6-hydroxypyrimidyl-4)alanine (A), and m-tyrosine (B).

A comparative study of amino acids I-Ic is in hand. The authors are very grateful to Prof. M. A. Prokof'ev for his continued interest in the present work.

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SYNTHESIS AND TRANSFORMATIONS OF FURAN DERIVATIVES

V. Synthesis of 4-Methylthiazolyl-(2)-Hydrazones of Aldehydes and Ketones of the Furan Series*

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Condensation of thiosemicarbazones of furfural, 3-(2-furyl)acrolein, as well as their 5-nitro derivatives with chloroacetone by boiling in alcohol or acetic acid gives the corresponding 4-methylthiazolyl-(2)hydrazones. 4-Methylthiazolyl-(2)-hydrazones of 5-nitro-2-acetylfuran and 5-nitro-2-furfurilydeneacetone can be prepared by condensing the corresponding thiosemicarbazones with chloroacetone by heating with glacial acetic acid containing fused sodium acetate.

4-Methylthiazolyl-(2)-hydrazones of aldehydes and ketones of the furan and 5-nitrofuran series (I-VI), analogs of previously described 4-(5'-nitrofuryl-2')thiazolyl-(2)-hydrazones [2], have been synthesized to study the relationship between chemotherapeutic action and chemical structure. Unlike the analogs mentioned, the new compounds do not have the furan ring linked directly to the thiazole ring, but situated at the end of the hydrazone group.

The above compounds were obtained by condensing chloroacetone with the corresponding thiosemicarbazones. Thiosemicarbazones of aldehydes of the furan series, of furfural, 3-(2-furyl)acrolein, and their 5-nitro derivatives could readily be brought to react with chloroacetone by boiling in alcohol or acetic acid, though the nitro derivatives required longer heating (up to 6 hr) than the furan compounds (10-15 min). Under the same conditions the thiosemicarbazones of ketones, of 2-furfurylideneacetone, its 5-nitro derivative, and 5-nitro-2-acetylfuran, did not react with chloroacetone,

*For Part IV see [1].