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PYRIMIDINE DERIVATIVES.

57.* NEW METHOD FOR THE SYNTHESIS OF PYRROLO[2,3-d]PYRIMIDINE

R. G. Melik-Ogandzhanyan, A. S. Gapoyan, V. É. Khachatryan, and V. S. Mirzoyan

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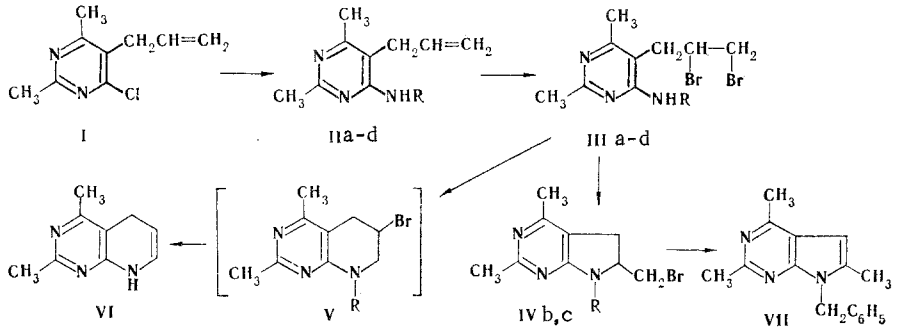
The action of bromine on 5-allyl-6-aminopyrimidines was studied. The formation of both a product of addition of bromine to the allylic bond and pyrrolo[2,3-d]-pyrimidines is possible, depending on the character of the substituent attached to the amino group. The structures of the synthesized compounds were confirmed by PMR and mass-spectrometric data.

In order to develop new methods for the synthesis of condensed pyrimidines [1-3], which are of interest as potential cancerolytics [4-6], in the present research we demonstrated the possibility of the preparation of a pyrrolo-[2,3-d]pyrimidine via the scheme



6-Aminopyrimidines (IIa-d) were obtained when 5-allyl-2,4-dimethyl-6-chloropyrimidine (I), which was synthesized by the method in [1] from the corresponding 6-hydroxypyrimidine, was heated with an alcohol solution of the amine in an autoclave at 150-200°C for 6-8 h.

The synthesis of IVb, c was carried out via a scheme similar to that which we described for furo[2,3-d]- and thieno[2,3-d]pyrimidine [1, 2]. The addition of bromine to the allyl group of IIb, c leads initially to the formation of intermediate dibromo products IIb, c, from which a molecule of hydrogen bromide is split out with the formation of a five-membered pyrrole ring.

In the case of 5-allyl-6-amino-2,4-dimethylpyrimidine (IIa) 2,4-dimethyl-5,8-dihydropyrido[2,3-d]pyrimidine (VI) is formed instead of the expected pyrrolo[2,3-d]pyrimidine (IVa). The reaction evidently proceeds through a step involving the formation of six-membered tetrahydropyrimidine V with subsequent splitting out of a molecule of hydrogen bromide to give VI.

*See [1] for Communication 56.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1686-1689, December, 1982. Original article submitted March 10, 1982.

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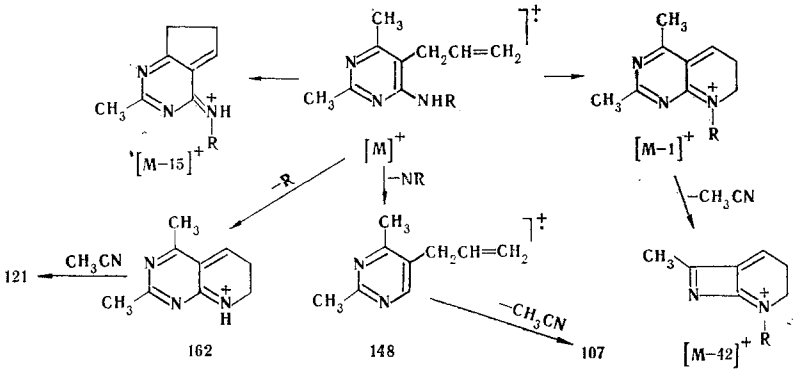
A pyrrole ring is not formed in the case of 6-β-hydroxyethylaminopyrimidine (IId), and the reaction stops at the step involving the formation of intermediate dibromo product IIId.

In the case of IVc we demonstrated the possibility of obtaining 2,4,6-trimethylpyrrolo-[2,3-d]pyrmidines (VII) by reaction of the corresponding bromomethyl derivatives with sodium methoxide.

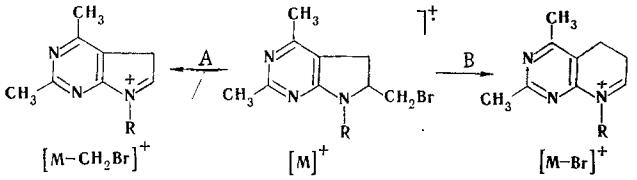
The structure of the synthesized compounds were confirmed by the PMR and mass-spectrometric data. In the PMR spectrum of pyrido[2,3-d]pyrimidine VI the methyl groups attached to the C_2 and C_4 atoms of the pyrimidine ring appear in the form of a singlets at 3.90 and 3.75 ppm, respectively. The protons of the methylene group form a group of lines at 4.38 ppm, while the vinyl protons form a multiplet centered at 5.80 ppm.

The dissociative ionization of the molecular ions of IIa-d evidently proceeds primarily via the scheme



The $[M - H]^+$ and $[M - R]^+$ ion peaks are very intense in all of the spectra; this can evidently be explained by the formation of a stable pyridine ring through the allyl group attached to the C_5 atom and the amino group attached to the C_6 atom of the pyrimidine ring. The peak with m/z 148 is due to a rearranged ion for IIb, the formation of which is similar to that described in [2]. Peaks of $[M - CH_2O]^+$, $[M - CH_2OH]^+$, and $[M - CH_2CH_2OH]^+$ ions and a peak of a rearranged ion, which is produced by ejection of a CH_2CH_2O group with migration of hydrogen to the charged fragment, the formation of which is associated with the R radical, are also observed for IId.

The scheme of the dissociative ionization for IVb, c is similar in many respects to the scheme presented in [1, 2] for furo- and thieno[2,3-d]pyrimidines. The molecular ions of IVb, c undergo fragmentation via two principal pathways A and B. The presence of the $[M - CH_2Br]^+$ ion peak is evidence in favor of the formation of a five-membered ring, since the formation of six-membered ring V should have excluded pathway A in the fragmentation of IVb, c.



EXPERIMENTAL

The PMR spectra of 7% solutions of the compounds in $CDCl_3$ were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the source at temperatures 25-30°C below the melting points of the investigated compounds and at an ionization energy of 30 eV. Chromatography was carried out on Silufol UV-254 plates in a methanol–dimethylformamide system (2:1).

5-Allyl-6-amino-2,4-dimethylpyrimidines (IIa-e). A 100-ml steel autoclave was charged wtih 1.82 g (0.01 mole) of 5-allyl-2,4-dimethyl-6-chloropyrimidine (I), 0.02 mole of the corresponding amine, and 40 ml of methanol, and the mixture was heated at 150-200°C for 6-8 h. It was then cooled, and the solvent was removed by distillation. Water (50 ml) was added to

TABLE 1. 5-Allyl-6-amino-2,4-dimethylpyrimidines (IIa-d)

Compound	mp, °C (ethanol)	R_f	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IIa	190—191	0,62	66,0	8,1	26,0	$C_9H_{13}N_3$	66,3	8,0	25,8	78
IIb	90—91	0,64	67,6	8,5	23,7	$C_{10}H_{15}N_3$	67,8	8,5	23,7	78
IIc	104—105	0,73	75,8	7,6	16,7	$C_{16}H_{19}N_3$	75,9	7,5	16,6	72
IId	105—106	0,40	63,8	8,3	20,2	$C_{11}H_{17}N_3O$	63,8	8,2	20,3	97

the residue, and the aqueous mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate, the solvent was removed by distillation, and the residue was distilled *in vacuo* (IIb) or crystallized with ether and removed by filtration. The products were recrystallized from alcohols (Table 1).

2,4-Dimethyl-5,8-dihydropyrido[2,3-d]pyrimidine (VIa). A solution of 3.2 g (0.02 mole) of bromine in 20 ml of chloroform was added dropwise in the course of 15 min to a solution of 3.36 g (0.02 mole) of IIa in 30 ml of chloroform, after which the solvent was removed by distillation, 30 ml of dimethylformamide (DMF) was added to the residue, and the mixture was refluxed for 20-30 min. The crystals that formed when the mixture was cooled were removed by filtration and dissolved in water, and the aqueous solution was neutralized with 20% ammonium hydroxide and extracted with chloroform. The extract was dried over sodium sulfate, the solvent was removed by distillation, and the residue was recrystallized from alcohol to give 2.6 g (82%) of a product with mp 164-165°C and R_f 0.65. Found: C 67.0; H 6.7; N 26.2%. $C_9H_{11}N_3$. Calculated: C 67.1; H 6.8; N 26.0%; M (by mass spectrometry) 161.

6-Bromomethyl-5,6-dihydro-2,4,7-trimethylpyrrolo[2,3-d]pyrimidine (IVb). A solution of 3.2 g (0.02 mole) of bromine in 20 ml of chloroform was added dropwise in the course of 15 min to a solution of 3.54 g (0.02 mole) of IIb in 30 ml of chloroform, after which the solvent was removed by distillation, 30 ml of DMF was added to the residue, and the mixture was refluxed for 30 min. The crystals of the hydrobromide of IVb that precipitated after cooling were removed by filtration and dissolved in water, and the aqueous solution was made alkaline to pH 10 with 20% ammonium hydroxide and extracted with chloroform. The extract was dried with sodium sulfate, the solvent was removed by distillation, and the residue was recrystallized from alcohol to give 2.4 g (72%) of a product with mp 127-128°C and R_f 0.61. Found: C 46.7; H 5.0; N 16.2%. $C_{10}H_{10}BrN_3$. Calculated: C 46.8; H 5.1; N 16.4%; M (by mass spectrometry) 255.

7-Benzyl-6-bromomethyl-2,4-dimethyl-5,6-dihydropyrrolo[2,3-d]pyrimidine (IVc). A solution of 3.2 g (0.02 mole) of bromine in 20 ml of chloroform was added dropwise in the course of 15 min to a solution of 5.06 g (0.02 mole) of IIc in 30 ml of chloroform, after which the solvent was removed by distillation, and the residue was refluxed in 40 ml of ethanol for 10-12 h. The crystals that formed when the mixture was cooled were removed by filtration, washed with ether, and dried to give 4.8 g (73%) of a product with mp 210-211°C and R_f 0.59. Found: C 58.0; H 5.2; Br 24.3; N 12.3%. $C_{16}H_{18}BrN_3$. Calculated: C 57.8; H 5.4; Br 24.10; N 12.6%; M (by mass spectrometry) 331.

7-Benzyl-2,4,6-trimethylpyrrolo[2,3-d]pyrimidine (VII). Sodium methoxide, prepared from 0.23 g (0.01 mole) of sodium and 20 ml of absolute methanol, was added to a solution of 1.6 g (5 mmole) of IVc in 10 ml of methanol, and the mixture was refluxed for 5-6 h. The solvent was removed by distillation, water was added to the residue, and the mixture was filtered to give 0.55 g (50%) of a product with mp 65-67°C and R_f 0.70. Found: C 76.3; H 6.9; N 16.5%. $C_{16}H_{17}N_3$. Calculated: C 76.5; H 6.8; N 16.7%; M (by mass spectrometry) 251.

5-(2,3-Dibromopropyl)-2,4-dimethyl-6-β-hydroethylaminopyrimidine (IIId). A solution of 1.6 g (0.01 mole) of bromine in 20 ml of chloroform was added dropwise in the course of 15 min to a solution of 2.07 g (0.01 mole) of IId in 30 ml of chloroform, after which the chloroform was removed by distillation, 30 ml of methanol was added to the residue, and the mixture was refluxed for 10-12 h. The methanol was removed by distillation, 20 ml of water was added to the residue, and the mixture was made alkaline to pH 7.5 by the addition of 20% ammonium hydroxide. The resulting oily precipitate was crystallized by cooling and trituration with a glass rod to give 2.4 g (67%) of a product with mp 119-121°C and R_f 0.60. Found: C 36.9: H 4.8; N 11.4%. $C_{11}H_{17}Br_2N_3O$. Calculated: C 36.2; H 4.6; N 11.2%; M (by mass spectrometry) 367.

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SYNTHESIS OF OPTICALLY ACTIVE 9-PURINYL-α-AMINO ACIDS

S. E. Poritere, Ya. Ya. Shluke, M. Yu. Lidak, and M. K. Kilevitsa

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A general method for the synthesis of optically active 9-purinyl-α-amino acids by condensation of 5-amino-4,6-dichloropyrimidine with α,ω-diamino carboxylic acids and subsequent cyclization of the N_ω-(5-amino-4-chloro-6-pyrimidinyl)-amino acids with triethyl orthoformate was developed. A number of 6-substituted α-amino-ω-(9-purinyl) carboxylic acids were obtained by nucleophilic substitution of the chlorine atom in the α-amino-ω-(6-chloro-9-purinyl) carboxylic acids.

We first synthesized 9-purinyl-α-amino acids by the cyanohydrin method [1], after which they were obtained by other researchers [2-4]; however, the syntheses of only racemic 9-purinyl-α-amino acids have thus far been described.

Interesting data regarding the biological activity of 9-purinylamino acids were recently obtained. Thus some of the derivatives isolated from the growing seeds of lupine are of interest as new cytokinins [5]. It has also been established that 9-adeninyl-α-alanine is a strong activator of the enzyme adenylate cyclase, which is responsible for the synthesis of cyclic AMP in the cell [6].

The goal of the present research was to develop a method for the direct synthesis of the optically active 9-purinyl-α-amino acids that are necessary for further biological studies.

We have already reported [7] a new method for the synthesis of 6-substituted 9-purinyl-α-amino acids that is based on the cyclization of N_ω-(5-amino-4-chloro-6-pyrimidinyl)diamino carboxylic acids with ethyl orthoformate; this method made it possible to obtain DL-α-amino-ε-(6-chloro-9-purinyl)caproic acid [7].

Further studies showed that the method is general in character and that by using the corresponding α,ω-diamino carboxylic acids one can synthesize 9-purinyl-α-aminovaleric acids (regarding the synthesis of which no data had been previously reported), as well as 9-purinyl-α-aminopropionic and -α-aminobutyric acids, which had previously been obtained by other methods [2-4].

Optically active 9-purinyl-α-amino acids can also be obtained by this new method by using L- or D-α,ω-diamino carboxylic acids as the asymmetric agent, and optically active N_α-substituted ω-(9-purinyl)amino carboxylic acids that are suitable for the subsequent synthesis of peptides can also be obtained by using N_α-substituted diamino carboxylic acids.

The starting compounds were N_ω-(5-amino-4-chloro-6-pyrimidinyl)diamino acids II, which were obtained by condensation of 5-amino-4,6-dichloropyrimidine (I) with the corresponding α,ω-diamino carboxylic acids.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
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