CYCLIZATION OF 4-AMINO-5-ACY LAMINO-6-FURFURY LAMINOPYRIMIDINES

V. M. Cherkasov and L. K. Kurilenko

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4,5-Diamino-6-furfurylaminopyrimidine reacts with butyric and valeric anhydrides to give the corresponding 5-N-acyl derivatives. Cyclization of 4-amino-5-butyramido-6-furfurylaminopyrimidine with butyric anhydride gives 6-butyramido-9-furfuryl-8-propylpurine, while cyclization with alcoholic alkali affords the 8-substituted kinetins 6-furfurylamino-8-propyl- and -8-butylpurines, as well as the isomeric 6-amino-8-propyl- and 6-amino-8-butyl-9-furfurylpurines.

Only one 8-alkyl-substituted kinetin (6-furfuryl-amino-8-methylpurine, or 8-methylkinetin) (I) has been described in the literature [1]. The synthesis of 8-alkylkinetins with a greater number of carbon atoms (8-propyl- and 8-butylkinetins, Va and Vb) for biological evaluation as kinins [2, 3] has been considered. The cyclization of 4, 5-diamino-6-furfurylaminopyrimidine (II) has been examined in this connection. Heating II with an excess of butyric or valeric anhydride caused considerable resinification, unlike the reaction with acetic anhydride [4], and the corresponding 8-alkylkinetins were not obtained.

Another possible method of synthesis of 8-alkylkinetins is by acylation of II under milder conditions, followed by cyclization of the 5-acyl derivatives (III). Acylation of II in benzene afforded 4-amino-5-butyramido-6-furfurylaminopyrimidine (IIIa), which on heating with butyric anhydride in the absence of a solvent gave a 55% yield of 6-butyramido-9-furfuryl-8-propylpurine (IVa) instead of 6-furfurylamino-8-propylpurine (Va), which was expected by analogy with the similar preparation of I. No other products could be isolated from the extremely resinous reation mixture.

The known methods [4-6] of cyclization of 4-amino-5-acylaminopyrimidines failed with IIIa and IIIb, giving in every case extremely resinous reaction mixtures. Cyclization was effected with alcoholic alkali, by the method described for 2-acetamido-3-amino-1, 4-naphthaquinone [7]. When the acyl derivatives IIIa and IIIb were heated with alcoholic caustic soda, the reaction proceeded in two ways. In each case both possible reaction products were formed, Va and Vb being obtained in 17 and 19% yields, and VIa and VIb in 75 and 78% yields, respectively.

The structure of IVa was confirmed by its insolubility in alkalis like 9-substituted purines, and by hydrolysis with 2 N caustic soda to VIa; product was identical to VIa obtained by cyclization of IIIa with alcoholic

alkali. VIa and VIb, being adenine derivatives, are readily acetylated by acetic anhydride to VIIa and VIIb. Compounds Va and Vb are not acetylated under these conditions with acetic anhydride, and are soluble in alkalis as is kinetin. The direction of this cyclization appears to depend mainly on the basicities of the primary and secondary amino groups participating in the reaction, since steric factors would favor cyclization involving the primary amino group, which is contrary to the experimental results.

EXPERIMENTAL

4,5-Diamino-6-furfurylaminopyrimidine (II). This was prepared in several stages from **4,6-dihydroxypyrimidine** and 2-furfurylamine [8,9].

4-Amino-5-butyramido-6-furfurylaminopyrimidine (IIIa) and 4-amino-6-furfurylamino-5-valeramidopyrimidine (IIIb). Compound II (1 g; 5 mM), butyric or valeric anhydride (6 mM) and benzene (30 ml) were boiled for 2 hr. The precipitate was filtered off and recrystallized from water. Yield of IIIa was 1.07 g (80%), colorless needles mp 201-202°. Found, %: C 56.37; H 6.38; N 25.63. Calculated for $C_{13}H_{17}N_5O_2$, %: C 56.71; H 6.22; N 25.44.

Yield of IIIb was 1.12 g (80%), colorless needles mp $180-182^{\circ}$. Found, %: C 58.19; H 6.84; N 24.28. Calculated for $C_{14}H_{19}N_5O_2$, %: C 58.11; H 6.61; N 24.20.

6-Butyramido-9-furfuryl-8-propylpurine (IVa). Butyric anhydride (3.8 g; 0.02 mole) and IIIa (3.3 g; 0.012 mole) were heated at 200° for 2 hr. Butyric acid was removed in a current of steam, and the residual resinous mass was separated, dried, and extracted with petroleum ether. Removal of the solvent left 2.2 g (54%) of IVa, mp 126-128°, colorless crystals (from petroleum ether—benzene). Found, %: C 62.23; H 6.17; N 21.46. Calculated for $C_{17}H_{21}N_5O_2$, %: C 62.26; H 6.46; N 21.39.

6-Amino-9-furfuryl-8-propylpurine (VIa). Compound IVa (3.8 g; 0.01 mole) was dissolved in 50 ml of 2 N caustic soda, and the solution was heated below the boiling point until separation of the precipitate of VIa was complete. Yield 2.9 g (96%), white acicular crystals, mp 170-171° (from water); mp 174-175° on rapid heating. Found, %: C 61.06, 61.16; H 5.74, 5.81; N 27.25, 27.14. Calculated for $C_{13}H_{15}N_5O$, %: C 60.68; H 5.87; N 27.22.

Cyclization of IIIa. Compound IIIa (2 g; 7mM) was boiled for 1 hr with a 1 N solution of caustic soda in aqueous ethanol (1:1). The ethanol was removed in vacuo, and the precipitate filtered off. There was obtained 1.4 g (76%) of VIa as colorless needles, mp 170-171° (from ethanol). Found, %: C 60.80; H 5.97; N 27.41. Calculated for $C_{13}H_{15}N_5O$, %: C 60.68; H 5.87; N 27.22. The compound was identical with a sample of material obtained by the hydrolysis of IVa. The alkaline filtrate from VIa was neutralized with hydrochloric acid to pH 7, and the white precipitate of 6-furfurylamino-8-propylpurine (Va) was filtered off. Yield 0.35 g (19%), mp 182-183° (from butanol). Found, %: C 60.73; H 5.84; N 27.18. Calculated for $C_{13}H_{15}N_5O$, %: C 60.68; H 5.87; N 27.22.

Cyclization of IIIb. This was carried out as in the preceding experiment. There was obtained 1.4 g (76%) of 6-amino-8-butyl-9-furfurylpurine (VIb), mp 144-145° (from water). Found, %: C 62.48; H 6.36; N 26.00. Calculated for $C_{14}H_{17}N_5O$, %: C 61.97; H 6.31; N 25.81. There was also obtained 0.3 g (17%) of 8-butyl-6-furfurylamino-purine (Vb), mp 199-200° (from butanol). Found, %: C 61.84; H 6.23; N 25.86. Calculated for $C_{14}H_{17}N_5O$, %: C 61.97; H 6.31; N 25.81.

6-Acetamido-9-furfuryl-8-propylpurine (VIIa). Acetic anhydride (1.3 g; 0.015 mole) and VIa (0.4 g; 0.0015 mole) were boiled gently for 1 hr. The acetic anhydride was removed in vacuo, and the residue recrystallized to give 0.42 g (90%) of VIIa, colorless needles, mp 158-160° (from water). Found, %: C 59.95; H 5.66; N 23.27. Calculated for $C_{15}H_{17}N_5O_2$, %: C 60.18; H 5.72; N 23.39.

6-Acetamido-8-buty!-9-furfurylpurine (VIIb). This was obtained in a similar manner to VIIa, from VIb (0.55 g; 0.002 mole), in a yield of 0.6 g (95%). Colorless needles (from water), mp 106-107°. Found, %: C 61.46; H 5.93; N 22.21. Calculated for $C_{16}H_{19}N_5O_2$, %: C 61.32; H 6.11; N 22.35.

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Institute of Organic Chemistry, AS Ukrainian SSR, Kiev