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A New Synthesis of Kinetin and Its Analogs

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A new two-step synthesis of kinetin and its analogs from adenine is reported. Adenine is acylated in good yield by anhydrides of aliphatic, aromatic or heterocyclic carboxylic acids. The amides so formed (I) are reduced to the corresponding amines (II). When insoluble intermediate complexes (*cf.* II-F) are not formed, the yields in the reduction step are satisfactory and the products are easily purified.

The announcement of the discovery[2] of the plant cell division factor kinetin was followed shortly[3] by a structure proof and a synthesis which established its identity as 6-(α-furylamino)purine.

The original synthesis was an adaptation of the procedure disclosed by Elion, *et al.*[4] for preparing 6-aminopurines; it employs the rather expensive 6-mercaptopurine as starting material. Methods of preparing *kinetin* and its analogs from 6-chloropurine[5,6] and from 4,6-pyrimidinedione[5] have also been described. We wish to report here a two-step synthesis from adenine,[7] which, with respect to cost and availability, is a more favorable initial reactant than those that have been used previously.

The 6-amino-group of adenine is first acylated by fusing adenine with an acid anhydride at *ca.* 140° (Method A) or by heating adenine with the anhydride in refluxing xylene as a medium (Method B). The yields by either method are good. The amides prepared in this study, together with pertinent data, are listed in Table I.

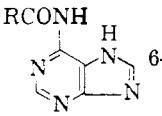
Typical examples of each method of preparation are given in the EXPERIMENTAL section.

The crude amides (I) were reduced to the amines (II) by means of lithium aluminum hydride in tetrahydrofuran (THF) first at room temperature and finally at reflux. This method appears to be of wide applicability: Table II summarizes the data on representative examples of 6-R-methylaminopurines so prepared, in which R is aliphatic, aromatic, or heterocyclic.

The yields are generally good, subject to the limitations that are usually encountered[9] when an insoluble intermediate is formed in the course of the reduction (II-F). There was no evidence that any of the double bonds of the purine nucleus had been reduced.

In small-scale experiments, in which a very large excess of THF was used (70 ml./g. of amide), the product, after decomposition of the excess lithium aluminum hydride, was found largely in the THF solution. In large-scale experiments employing a smaller excess of THF (*ca.* 32 ml./g. of amide), the product appeared mainly in the form of a lithium and/or aluminum salt in the insoluble inorganic

TABLE I



6-ACYLAMINOPURINES

Cpd.	R	Method of Prep.	Crude Yield, %	Solvent for Cryst.	M.P.,[a] °C.	Analyses[b] Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
I-A	Methyl[c]	A	75	HOAc							
I-B	Phenyl[c]	A	93.5	EtOH	242–243						
I-C	2-Furyl[d]	A	83.2	H_2O	214–216	52.40	3.08	30.55	52.45	3.17	30.90
I-D	2-Thienyl	A	56[e]	HOAc	248.5–249.5	48.97	2.88	28.56	48.78	2.88	28.40
I-E	o-Tolyl	A	56.5[e]	EtOH	194.2–194.8	61.63	4.38	27.66	61.78	4.55	27.79
I-F	2-Pyridyl	B	76–80	EtOH	285–286.2	54.96	3.36	34.99	55.53	3.33	35.19

[a] Corrected. [b] Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. [c] Previously reported by Kossel, *Z. physiol. Chem.*, **12**, 246 (1888). [d] Dried at 110° *in vacuo* just before analysis. [e] After recrystallization.

(1) The encouragement given by Dr. W. G. Bywater, S. B. Penick and Co., is gratefully acknowledged.

(2) Miller, Skoog, Saltza, and Strong, *J. Am. Chem. Soc.*, **77**, 1392 (1955).

(3) (a) Miller, Skoog, Okumura, Saltza, and Strong, *J. Am. Chem. Soc.*, **77**, 2662 (1955); (b) *J. Am. Chem. Soc.*, **78**, 1375 (1956).

(4) Elion, Burgi, and Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

(5) Daly and Christensen, *J. Org. Chem.*, **21**, 177 (1956).

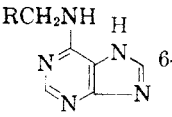
(6) Bullock, *et al.*, Abstracts, *Dallas meeting*, American Chemical Society, p. 3M (1956).

(7) Miller, *et al.*[3b] showed *qualitatively* that kinetin was formed in the reaction between adenine and furfuryl chloride.

(8) Skinner and Shive, *J. Am. Chem. Soc.*, **77**, 6692 (1955).

(9) Brown in Adams, *Org. Reactions*, **6**, 474 (1951).

TABLE II



6-R-METHYLAMINOPURINES

Cpd.	R	Crude Yield, %	Solvent for Cryst.	M.P.[a] °C.	Analyses[b] Calc'd C	Calc'd H	Calc'd N	Found H	Found H	Found N
II-A	Methyl[c]	34	H_2O	237–237.5	51.51	5.58	42.92	51.47	5.40	42.98
II-B	Phenyl[d]	87	20% EtOH	232.5	63.98	4.92	31.09	64.15	5.00	31.03
II-C	2-Furyl[2,3,7]	70.4	EtOH	270–272	55.81	4.03	32.54	56.09	4.15	32.32
II-D	2-Thienyl[d]	48	95% EtOH	249–249.5	51.93	3.93	30.28	52.28	3.75	30.52
II-E	o-Tolyl	62	90% EtOH	243.6–244.6	65.25	5.48	29.40	65.41	5.41	29.29
II-F	2-Pyridyl[e]	20	EtOH	236–238	58.39	4.46	37.15	58.89	4.23	36.10[f]

[a] Corrected. [b] Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. [c] Previously reported.[4] [d] Reported[8] after this work was completed. [e] Reported[8] m.p. 257° on Fisher block. Our sample melted at 236–238° in a capillary as did a sample kindly supplied by Dr. Skinner; no depression in the m.p. of the mixture. [f] *Cf.* comments by Elion, *et al.*[4] on nitrogen analyses in this series.

hydroxide fraction. Examples of the procedure for recovering the final product from each type of reaction mixture are given in the EXPERIMENTAL section.

EXPERIMENTAL

1. *Preparation of the amides* (I). *Method A.* A mixture of 1.35 g. (0.01 mole) of adenine and 3.0 g. (0.015 mole) of α-furoic anhydride was heated in an oil-bath one hour at 80° and then four hours at 140°. At the higher temperature a homogenous melt was obtained.[10] The mixture was cooled, diluted with 50 ml. of water, and heated under reflux for one hour. It then was partially cooled, neutralized by the addition of sodium bicarbonate, and chilled. The crude amide (I-C) was removed by filtration, washed with cold water, and dried *in vacuo* over phosphorus pentoxide at room temperature.

Method B. Picolinic anhydride[11] (*ca.* 5 g.) dissolved in 50 ml. of dry xylene was stirred with 1.5 g. of adenine and heated under reflux for one hour. The mixture was cooled and the gummy precipitate was removed by filtration and digested with a slight excess of dilute sodium bicarbonate, whereupon it crystallized (I-F).

2. *Reduction of the amides* (I) *to the amines* (II). *Small-scale.* One gram of 6-(α-furoylamino)purine (I-C) was added portionwise to a stirred solution of 0.75 g. of lithium aluminum hydride in 70 ml. of THF at room temperature. The mixture was stirred for four hours, allowed to stand without stirring for 64 hours, and finally was heated under reflux for two hours. The excess lithium aluminum hydride remaining in the cooled mixture was decomposed by the dropwise addition of water. The inorganic hydroxides were removed by filtration and washed with 20 ml. of THF. The combined organic solutions were distilled to dryness *in vacuo*. The residual solid was crystallized from ethanol. There was obtained, in several crops, 0.480 g. (50.5%)[12] of kinetin (II-C). A sample recrystallized from absolute ethanol melted at 270–272° (corr; sealed tube) and showed a maximum at 268 mμ (E = 18,700) and a minimum at 234 mμ (E = 3,160).

Large-scale. To a solution of 88 g. (2.32 moles) of lithium aluminum hydride in 7 liters of THF contained in a 12-liter flask was added with stirring 221 g. (0.928 mole) of 6-(α-benzoylamino)purine (I-B) in the course of 95 minutes. The heat of reaction brought the solvent to reflux. Stirring was continued for 30 minutes. The mixture then was allowed to stand at room temperature for 63 hours and finally was heated under reflux for 90 minutes. After the reaction mixture was cooled the excess lithium aluminum hydride was decomposed by the cautious addition of 280 ml. of ethyl acetate followed by 170 ml. of water. The precipitate was removed by filtration and washed with THF. The filtrates were combined; the solvents were removed by distillation while water was being simultaneously added to the flask. Upon cooling the aqueous solution (*ca.* 700 ml.) 21.2 g. of 6-(α-benzylamino)purine (II-B) precipitated. Neutralization of the (alkaline) filtrate yielded an additional 17.5 g. of product.

The THF-insoluble fraction removed above was extracted continuously with alcohol in a Soxhlet apparatus for 16 hours. The extract was taken to dryness. The residue was dissolved in water and neutralized, whereupon 142.2 g. of II-C precipitated.

The total crude product (180.9 g., 87%) was dissolved in 1500 ml. of water by the addition of strong sodium hydroxide. The alkaline solution was charcoaled and filtered. Adjustment of the filtrate to *p*H 8–8.5 precipitated 180.7 g. of off-white product melting at 230–232°.

NEWARK, N. J.

(10) In the preparation of other amides of this series, the mixture passed through a fluid phase and then re-solidified.

(11) Prepared by an adaptation of the procedure Schrecker and Maury, *J. Am. Chem. Soc.*, **76**, 5803 (1954), reported for nicotinic anhydride.

(12) The yield reported in Table II is based on a large-scale run.