EXPERIMENTAL

The pure 2,3-lutidine was a Matheson product. The infrared spectra were determined by a Perkin-Elmer Model 21 Spectrophotometer equipped with a sodium chloride prism.

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Reduction of 6-Aroylaminopurines with Lithium Aluminum Hydride

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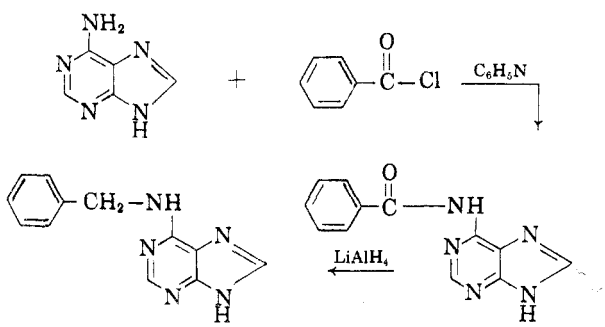
6-Furfurylaminopurine (kinetin) and several other closely related analogs have been prepared by condensation of 6-methylmercaptopurine and 6-chloropurine with appropriate amines.[1,2,3] The 6-substituted purine derivatives required for these methods are obtained with considerable difficulty. We have investigated the use of adenine as a starting material for the preparation of kinetin and 6-benzylaminopurine. The synthesis requires only two steps from readily available starting materials.



The benzoylation of adenine with benzoic anhydride has been described by Kossel[4] who reported no yield. We have found that benzoyl chloride in the presence of pyridine gives the benzamido compound in satisfactory yields. A side reaction is dibenzoylation in both the 6-amino group and in an unidentified position.[5] The aroyl group appears to be hydrolyzed from the unidentified position with water which simplifies the preparation of the desired monosubstituted derivative.

The procedure for the reduction was patterned after a procedure found useful by Baker and coworkers[6] in the pyrimidine series.

EXPERIMENTAL[7]

6-Benzoylaminopurine. Twenty-six and two-tenths g. (0.222 mole) of benzoyl chloride was added to a suspension of 10 g. (0.074 mole) of adenine in 50 ml. dry pyridine. The reaction mixture was refluxed 2 hr. The excess pyridine was distilled from the then homogeneous solution leaving a semicrystalline mass. The crude product was triturated with warm sodium bicarbonate solution which caused the separation of an oily phase. When the aqueous suspension was shaken with chloroform the amide precipitated. The crystals were filtered off and washed with water. This product weighed 7.0 g. and melted at 240°. The chloroform solution was decolorized with "Darco G-60" activated charcoal and evaporated to dryness. The residue was crystallized from 30 ml. ethanol to yield 15.2 g. of impure amide, m.p. 120–230°. The crude product was extracted in a Soxhlet extractor with ligroin and the insoluble fraction recrystallized from methyl Cellosolve to yield pure crystals, m.p. 240–240.5°.[8] The total yield of pure product was 12.8 g. (0.254 mole), 72.5%.

Anal. Calcd. for $C_{12}H_9N_5O$: C, 60.24; H, 3.79; N, 29.28. Found: C, 60.48; H, 3.85; N, 29.72.

6-Benzylaminopurine. A suspension of 0.5 g. lithium aluminum hydride in 10 ml. *N*-methylmorpholine was added dropwise to a warm, well stirred solution of 2.39 g. (10 millimoles) 6-benzoylaminopurine in 25 ml. pyridine. The reaction was strongly exothermic and the reaction mixture became brown. The mixture was stirred at room temperature 1 hr. and then at 100° for 1 hr. The solvents were distilled off under reduced pressure (water aspirator). The residue was triturated with 50 ml. of 0.1*N* sodium hydroxide and filtered. Neutralization of the filtrate gave 1.34 g. of a mixture of starting material and product. The mixture was shaken with 20 ml. 0.1*N* hydrochloric acid and filtered. The filter cake was washed with 0.1*N* hydrochloric acid. The unreacted starting material left on the filter weighed 0.62 g. (2.63 millimoles), 26.3% and m.p. 240–240.5°. The acid filtrate was neutralized with sodium hydroxide. The precipitated product was filtered off and washed copiously with water to yield 0.71 g. (3.15 millimoles, 31.5%) of white solid, m.p. 218–220°. Recrystallization from 4 ml. methyl Cellosolve gave 0.3 g. (1.33 millimoles, 13%) of pure product, m.p. 230–231°. A mixed melting point with an authentic sample of 6-benzylaminopurine[8] showed no depression.

6-Furoylaminopurine. A mixture of 10 g. (0.074 mole) adenine, 19.2 g. (0.148 mole) furoyl chloride and 50 ml. pyridine was heated at 100–110° for 1 hr. and the pyridine distilled off under reduced pressure (water aspirator). The residue was crystallized from 50 ml. acetonitrile and then recrystallized from water to yield 9.5 g., m.p. 174–180°. Recrystallization from a water-acetonitrile mixture followed by a recrystallization from acetic acid gave pure product, m.p. 209–210°. The yield of pure material was 4.1 g. (0.179 mole, 24%).

Anal. Calcd. for $C_{10}H_7N_5O_2$: C, 52.40; H, 3.08; N, 30.56. Found: C, 52.74; H, 2.98; N, 30.68.

6-Furfurylaminopurine (kinetin). A suspension of 1 g. (25 millimoles) of lithium aluminum hydride of 95%

(1) C. O. Miller, F. Skoog, F. S. Okumura, M. H. von Saltza, and F. Strong, *J. Am. Chem. Soc.*, **77**, 2662 (1955).

(2) C. G. Skinner and W. Shive, *J. Am. Chem. Soc.*, **77**, 6692 (1955).

(3) M. W. Bullock, J. J. Hand, and E. L. R. Stokstad, *J. Am. Chem. Soc.*, **78**, 3693 (1956).

(4) A. Kossel, *Z. Physiol. Chem.*, **12**, 247 (1888).

(5) L. Birkofer, *Ber.*, **76B**, 769 (1943) reported that acylation of adenine with acyl anhydrides gave a disubstituted product which could be easily hydrolyzed to the 6-acylaminopurine.

(6) B. R. Baker, R. E. Schaub, and J. P. Joseph, *J. Org. Chem.*, **19**, 638 (1954).

(7) Melting points are uncorrected. The microanalyses were done by Mr. L. Brancone and staff of our research division.

(8) A. Kossel, ref. 4, gave m.p. 234–235°. P. A. Levine and R. S. Tipson, *J. Biol. Chem.*, **121**, 143–145 (1937) gave m.p. 237–238°.

purity in 10 ml. ether was added dropwise to a stirring solution of 2.29 g. (10 millimoles) of 6-furoylaminopurine in 25 ml. pyridine. The reaction was highly exothermic and the mixture became dark and eventually too thick to stir. The reaction mixture was maintained at 70° for 1 hr. and allowed to cool. The mixture was transferred to a larger flask with a little methanol. The solvents were distilled off under reduced pressure (water aspirator) and the residue extracted with 0.1*N* sodium hydroxide. Neutralization of the alkaline extract precipitated the product. The yield was 0.47 g. (2.18 millimoles, 21.8%), m.p. 263–265°. Recrystallization from methyl Cellosolve gave pure kinetin, m.p. 267–268° (sealed capillary) (1, 2, 3). A mixed melting point with an authentic sample showed no depression.

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Structure of "3-Phenylthiazetidine"

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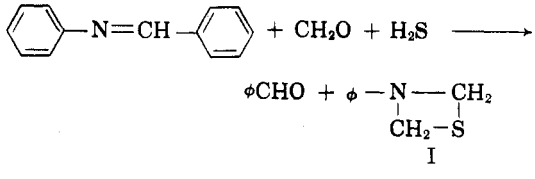
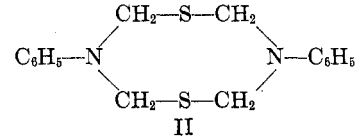
A recent article[1] described the reaction of formaldehyde, hydrogen sulfide, and *N*-benzylidene aniline, and reported that the structure of the product is that of "3-phenylthiazetidine." This preparation was repeated.



I

A product was isolated which appeared to be the one described earlier[1] although the melting point was somewhat higher. The infrared spectrum (Fig 1) showed clearly that —NH—, —SH, —OH and C=O were absent, and that C=S, C=C, and C=N were probably absent. A nuclear magnetic resonance spectrum showed only two types of hydrogen, one of which was obviously phenyl hydrogen. Combustion analysis agreed quite closely with the formula C_8H_9NS, (mol. wt. 151). However, ebullioscopic molecular weight determinations showed an average value of 308 in ethanol, indicating that the actual empirical formula should be $C_{16}H_{18}N_2S_2$.

On the basis of the above information, we suggest that the product originally formulated as 3-phenylthiazetidine (I) is, in fact, the highly symmetrical 3,7-diphenyl-1,5-dithia-3,7-diazacyclooctane (II).



II

EXPERIMENTAL

"3-Phenylthiazetidine." Hydrogen sulfide was bubbled into 250 g. of 38% aqueous formaldehyde solution until 20 g. was absorbed. A solution of 100 g. of benzylidene aniline in 850 ml. of absolute alcohol was prepared and mixed with the hydrogen sulfide–formaldehyde solution. As the two solutions were mixed, a strong blue-green color developed which gradually faded. The mixture was maintained at room temperature for 24 hr. During the course of this time a crystalline solid precipitated from the solution. This was filtered and refluxed with 1 l. of absolute methyl alcohol. After cooling, the solution was filtered and the solid product was dried. It weighed 75 g. and melted in the range 173–178° on a Kofler hot stage between crossed Polaroids. This substance was recrystallized from chloroform to give crystals melting sharply at 186°. Melting was preceded by a phase transformation from plates to needles beginning at about 170°.

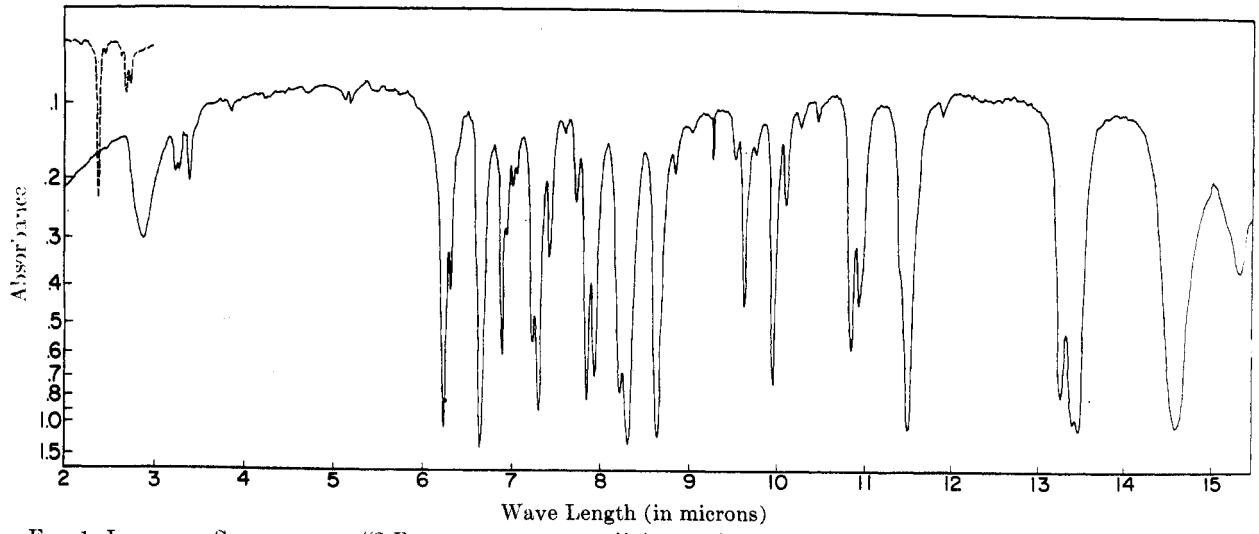


FIG. 1. INFRARED SPECTRUM OF "3-PHENYLTHIAZETIDINE." (--------) 100 mg. of compound/cc. of chloroform; (———) KBr pellet (unavoidable traces of water in salt). Concentration of solid in KBr pellet qualitatively the same as chloroform solution

Anal. Calcd. for C_8H_9NS: C, 63.55; H, 6.00; mol. wt.

(1) Collins and Graymore, *J. Chem. Soc.*, 4089 (1953).