Anal. Calcd. for $C_{22}H_{17}NO$: N, 4.50. Found: N, 4.41, 4.36.

1-Isoquinolyllithium and α,α-diphenyl-1-isoquinolinemethanol. The preparation of the 1-isoquinolyllithium was carried out in the same manner as that described for the 2-quinolyllithium.

To the 1-isoquinolyllithium, there was added 4.5 g. (0.025 mole) of benzophenone in 100 ml. of anhydrous ether. The temperature of the reaction mixture rose to −40° and remained there for the rest of the addition. After the introduction of 75 ml., Color Test I[10] was negative. The color of the reaction mixture was blue-black, and a considerable amount of white solid had separated. After hydrolysis, the ether extract was dried over sodium sulfate. On concentration of the ether solution, the crude product was obtained in a yield of 5.33 g. (68%). After crystallization from ethanol, the melting point of the pure compound was 144–145°.

Anal. Calcd. for $C_{22}H_{17}NO$: N, 4.50. Found: N, 4.40, 4.42.

Carbonation of 2-quinolyllithium at −50°. The 2-quinolyllithium which had been prepared from 5.2 g. (0.025 mole) of 2-bromoquinoline at −50° was carbonated by pouring jet-wise onto a slurry of dry ice–ether. The carbonation mixture was extracted with 100 ml. of 10% sodium hydroxide solution. The ether layer was separated, and the basic portion extracted with 50 ml. of ether. The ether extracts were combined and dried over anhydrous sodium sulfate.

The basic layer was treated with charcoal, filtered, concentrated, and acidified to a *p*H of 3. Quinaloic acid was isolated in a yield of 0.9%.

The ether extract was concentrated by distillation of the solvent. The residue was crystallized from ethanol to give 1.5 g. (34%) of 2,2′-diquinolyl ketone which melted at 166–167° (lit. value 165–166°).[11] The oxime was prepared and melted at 205–206° (lit. value 201–202°).[11]

Carbonation of 2-quinolyllithium at −100°. The 2-quinolyllithium was prepared in a flask which was equipped with a stopcock at the bottom in exactly the same manner as above. The stopcock was opened, and the 2-quinolyllithium flowed over the dry ice–ether slurry which was cooled to −100° by means of an ether-ethanol liquid nitrogen slurry.

The carbonation mixture was treated with 100 ml. of 10% sodium hydroxide. This basic layer which was separated from the ether layer was treated with charcoal, filtered, acidified to a *p*H of 3, and concentrated. The acid which was obtained in a yield of 1 g. (25%) melted at 158.0–158.5°. A mixed melting point with an authentic sample of quinaldic acid was not depressed.

From the ether extract, there was obtained 2,2′-diquinolyl ketone in a yield of 0.6 g. (21%).

Carbonation of 1-isoquinolyllithium. The procedure was identical to that described for 2-quinolyllithium. The yield of 1,1′-diisoquinolyl ketone was 2 g. (44%). The melting point was 198–199°.

Anal. Calcd. for $C_{19}H_{12}N_2O$: N, 9.85. Found: N, 9.96, 10.07.

The oxime was prepared in a yield of 0.44 g. (92%) and melted between 252.5–253.0°.

Anal. Calcd. for $C_{19}H_{13}N_3O$: N, 14.04. Found: N, 13.88, 13.82.

Preparation and carbonation of 4-isoquinolyllithium. Into a three necked 500-ml. round bottomed flask, there was introduced 0.025 mole of *n*-butyllithium in 50 ml. of anhydrous ether. This solution was cooled to −50° by means of a dry ice–acetone bath, and 5.2 g. (0.025 mole) of 4-bromoisoquinoline was added as a solid. The color of the reaction mixture became yellow. Color Test II was negative[9] within 10 min., and Color Test I was positive.[10] The 4-isoquinolyllithium was carbonated by the usual procedure and worked up to give 1.93 g. (46%) of 4-isoquinolinecarboxylic acid which melted at 246–248°. A mixed melting point with an authentic specimen was not depressed.

(11) Scheibe and Schmidt, *Ber.*, **55**, 3159 (1922).

The organic layer was concentrated, but no ketone was isolated.

Carbonation of 3-quinolyllithium. The 3-quinolyllithium was prepared and carbonated by the same procedure as described for 4-isoquinolyllithium. On acidification of the basic extract, there was obtained 2.2 g. (50%) of 3-quinolinecarboxylic acid which melted at 269–270°. A mixed melting point with a known sample was not depressed. On the work-up of the ether extract, there was no ketone isolated.

Preparation of phenyllithium from chlorobenzene in tetrahydrofuran. Into a 500-ml. three necked round bottomed flask, there was introduced 100 ml. of anhydrous tetrahydrofuran[12] and 0.29 g.-atom of lithium wire which was cut into small pieces (1/4″). To this mixture which was stirred and cooled by an ice bath to 7°, there was added dropwise a solution of 0.1 mole of chlorobenzene (11 g.) in 52 ml. of tetrahydrofuran. The addition was so regulated that it required 45 min. After the addition of 10 ml., the temperature of the reaction mixture began to slowly rise and the cloudy mixture became light red. The temperature was maintained at 15° for the remainder of the addition at which time the color was wine red. Color Test II was positive.[9] The reaction mixture was carbonated and worked up in the usual way.

The basic extract was acidified to given an oil which solidified when dry air was blown over its surface. The yield of crude benzoic acid was 5.5 g. (54%), melting at 114–118°. A mixed melting point of the purified acid and an authentic specimen of benzoic acid showed no depression.

Preparation of 2-quinolyllithium in tetrahydrofuran at −50° and carbonation. This reaction was carried out exactly as described for the preparation of 2-quinolyllithium in diethyl ether except that tetrahydrofuran was employed as the solvent. The reaction mixture was carbonated by pouring jet-wise onto a dry ice–tetrahydrofuran slurry and worked up by the usual procedure.

The basic extract upon acidification to a *p*H of 3 and concentration gave 2.2 g. (50%) of 2-quinolinecarboxylic acid which melted at 156–157°. A mixed melting point with an authentic specimen was undepressed. Two other runs gave the same results.

The organic layer was dried and concentrated, but no ketone was isolated.

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AMES, IOWA

(12) The tetrahydrofuran was dried and purified by first shaking with sodium hydroxide pellets, refluxing over sodium metal for several hours and finally distilling immediately before use from lithium aluminum hydride.

Condensations of Unsymmetrical Ketones. IV. Participation of Methyl and Methylene Groups in Condensation Reactions

RAYMOND P. MARIELLA AND EDITH GODAR[1]

Received October 5, 1956

In the condensation of unsymmetrical ketones with various reagents, varying reports have been published concerning the site of reaction.[2]

(1) Taken in part from the M.S. thesis of Edith Godar.

(2) (a) Benary, *Ber.*, **59**, 2198 (1926). (b) Tracy and Elderfield, *J. Org. Chem.*, **6**, 70 (1941). (c) Hauser and Adams, *J. Am. Chem. Soc.*, **66**, 345 (1944). (d) Mariella, *J. Am. Chem. Soc.*, **69**, 2670 (1947). (e) Royals and Covington, *J. Am. Chem. Soc.*, **77**, 3155 (1955). (f) Cason and Chang, *J. Org. Chem.*, **21**, 449 (1956).

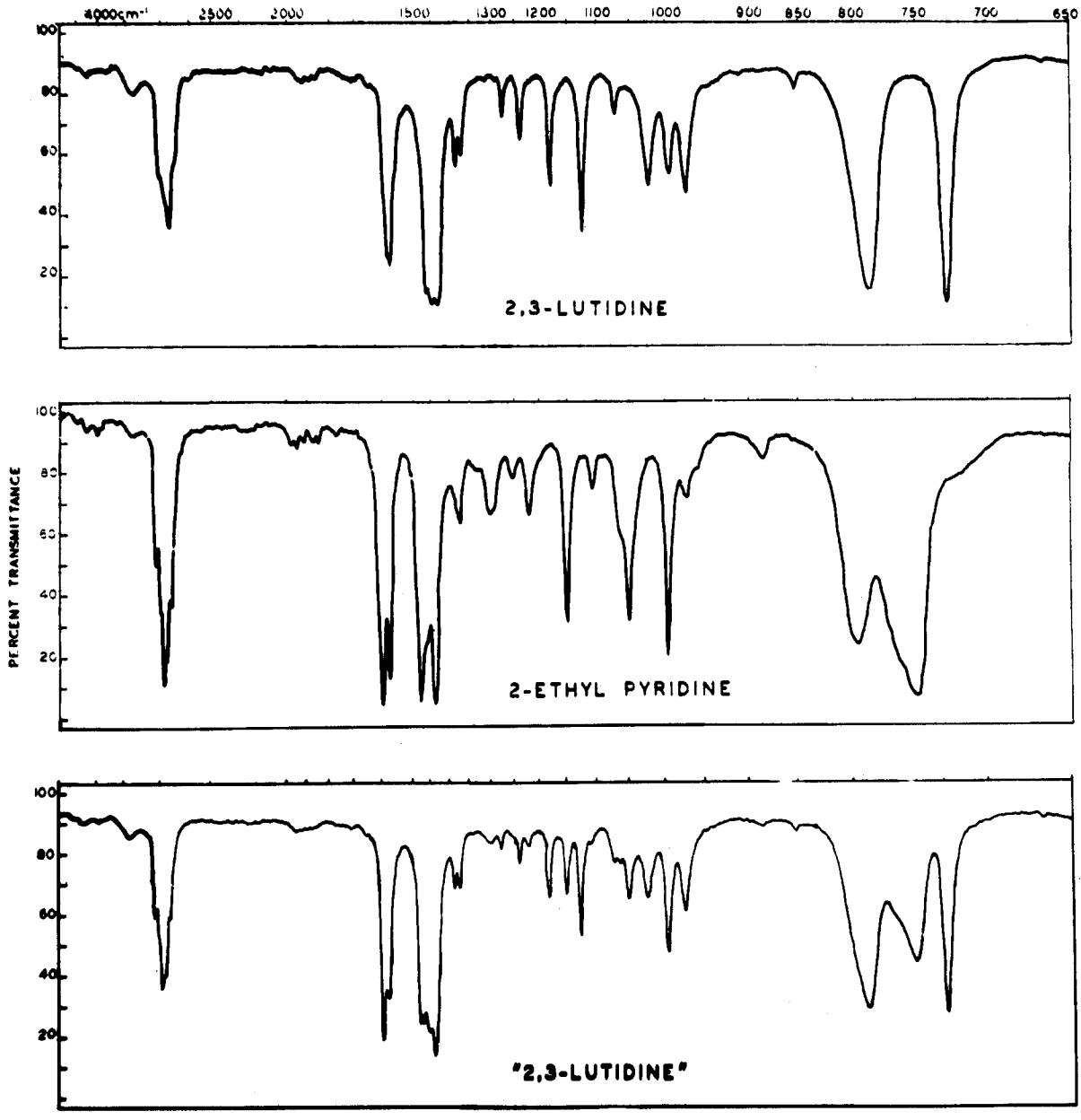

FIG. 1. INFRARED SPECTRA

The difficulty with past chemical evidence is that various steps were involved, during which one of the isomers was lost by a purification process.

Using the chemical approach,[2d] methyl ethyl ketone was condensed with ethyl formate and the crude product condensed with cyanoacetamide. In all subsequent reactions, no attempts were made to purify the crude material which was formed, and this crude isolated product was carried from step to step. The final 2,3-lutidine boiled at 162° at atmospheric pressure. The equivalent weight (perchloric acid titration in glacial acetic acid) was 110.2 (theoretical 107.15).

A comparison of the infrared spectrum of our "2,3-lutidine" with that of a carefully prepared sample of 2,3-lutidine obtained from coal tar fractionation has now shown that our sample contained about 40% 2-ethyl pyridine, thus corroborating previous work,[2e,2f] showing that both methyl and methylene groups do participate in condensation reactions of unsymmetrical ketones.

The impure lutidine showed bands at 1105 cm.$^{-1}$, 1050 cm.$^{-1}$, and an unresolved doublet with the strongest branch at 752 cm.$^{-1}$. These bands are characteristic of 2-alkyl pyridines.[3] The pure 2,3-lutidine did not exhibit these absorption bands. Fig. 1 shows the infrared curves of 2,3-lutidine, 2-ethylpyridine, and our "2,3-lutidine."

(3) We are indebted to Dr. Frank Cislak of Reilly Tar and Chemical for the sample and spectra of 2-ethylpyridine

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.

CHEMISTRY DEPARTMENT
LOYOLA UNIVERSITY
CHICAGO, ILL.

Reduction of 6-Aroylaminopurines with Lithium Aluminum Hydride

MILON W. BULLOCK, JOHN J. HAND, AND E. L. R. STOKSTAD

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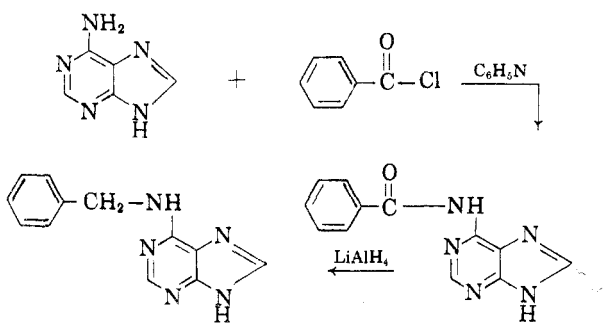
6-Furfurylaminopurine (kinetin) and several other closely related analogs have been prepared by condensation of 6-methylmercaptopurine and 6-chloropurine with appropriate amines.[1,2,3] The 6-substituted purine derivatives required for these methods are obtained with considerable difficulty. We have 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°.