

literature. Since all of the ketones are known their preparations can be found elsewhere.

Kinetics. The kinetic method was the same used previously.¹ In all cases the rate constants were calculated from a second order rate plot.

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Studies in Purine Chemistry. V. 7-Methyladenine-3-*N*-oxide¹

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Of the four possible structural types of purine-mono-*N*-oxides, representatives of only the 1- and 7-oxides have been reported.² The present paper describes the synthesis and properties of 7-methyladenine-3-*N*-oxide.

Although reduction of 1-methyl-4-nitro-5-cyanoimidazole (I) with Raney nickel is known to yield 1-methyl-4-amino-5-cyanoimidazole (III),³ we have found that yields in the reduction are variable and dependent upon the quality of the Raney nickel employed. In an attempt to improve on this conversion by the use of other catalysts, reduction of I was carried out with platinum oxide. Absorption of hydrogen either in ethanol or in ethanolic hydrogen chloride solution was complete within 8 minutes, but the reduction product proved to be 1-methyl-4-hydroxylamino-5-cyanoimidazole (II). Complete reduction to III had occurred only to a negligible (2.5%) extent. The structure of II was readily confirmed by further reduction with hydrogen in the presence of Raney nickel to 1-methyl-4-amino-5-cyanoimidazole (III).

Attempted cyclization of II by heating with formamide led only to extensive decomposition, but smooth cyclization to 7-methyladenine-3-*N*-oxide (IV) was effected by refluxing II in ethanol solution with formamidine acetate. 7-Methyladenine-3-*N*-oxide (IV) was similar in properties to previously described purine-1-*N*-oxides² in the following respects: (a) it was extremely hygroscopic and readily formed a stable monohydrate (b) it was appreciably more soluble in water than the parent purine, and (c) its ultraviolet absorption spectrum in dilute sodium hydroxide solution

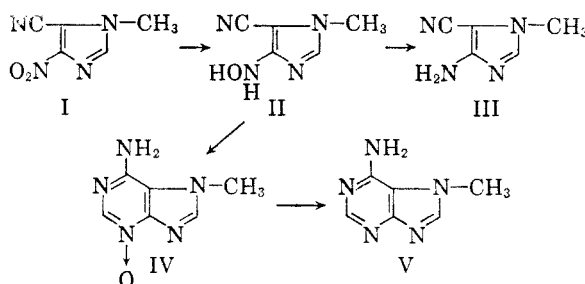
(1) This investigation was supported by a research grant (C-2551-PET) to Princeton University from the National Cancer Institute of the National Institutes of Health.

(2) For a summary of and appropriate references to previous work in this field, see the accompanying paper: E. C. Taylor, C. C. Cheng, and O. Vogl, *J. Org. Chem.*, **24**, 2019 (1959).

(3) R. N. Prasad and R. K. Robins, *J. Am. Chem. Soc.*, **79**, 6401 (1957).

showed two absorption maxima, the more intense peak being at the shorter wave length. Compound IV also exhibited two absorption maxima in 0.1 *N* hydrochloric acid solution, in contrast to adenine-1-*N*-oxide, which has been reported to have only one maximum in this solvent.⁴

The structure of 7-methyladenine-3-*N*-oxide follows not only from its method of preparation and its physical properties, but also from its facile reduction with hydrogen and Raney nickel to 7-methyladenine. It is of interest to note that similar conditions, which have been successfully employed for the reduction of adenine-1-*N*-oxide to adenine,⁵ were without effect on hypoxanthine-1-*N*-oxide.² Apparently the N—O bond in hypoxanthine-1-*N*-oxide (which is a cyclic hydroxamic acid) is appreciably stronger than the N—O bond of the adenine-*N*-oxides.



EXPERIMENTAL⁶

1-Methyl-4-hydroxylamino-5-cyanoimidazole (II). A solution of 10 g. of 1-methyl-4-nitro-5-cyanoimidazole in 200 ml. of ethanol containing 1 g. of platinum oxide was hydrogenated at room temperature and 3 atmospheres pressure until hydrogen absorption ceased (about 8 minutes). The reduction mixture was heated to boiling, filtered from the catalyst, and the filtrate chilled to give 6.0 g. (66%) of 1-methyl-4-hydroxylamino-5-cyanoimidazole as pale yellow needles which were recrystallized from ethanol; m.p. 178° (dec.).

Anal. Calcd. for C₈H₈N₄O: C, 43.5; H, 4.4; N, 40.6. Found: C, 43.8; H, 4.2; N, 40.4.

Evaporation of the filtrate yielded 0.2 g. (2.5%) of 1-methyl-4-amino-5-cyanoimidazole, identical with an authentic sample.³

Reduction of 1-Methyl-4-hydroxylamino-5-cyanoimidazole to 1-Methyl-4-amino-5-cyanoimidazole (III). A solution of 2.0 g. of 1-methyl-4-hydroxylamino-5-cyanoimidazole in 30 ml. of ethanol was hydrogenated in the presence of 2 g. of Raney nickel catalyst (wet with ethanol) at room temperature and at 3 atmospheres pressure for 12 hr. The reduction mixture was filtered from the catalyst, the filtrate concentrated under reduced pressure and the residue recrystallized from benzene to give 0.65 g. (37%) of light yellow crystals, m.p. 178–179, identical in all respects with an authentic sample of 1-methyl-4-amino-5-cyanoimidazole.³

*7-Methyladenine-3-*N*-oxide (IV).* A solution of 5 g. of 1-methyl-4-hydroxylamino-5-cyanoimidazole and 6.5 g. of

(4) M. A. Stevens and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 2759 (1958).

(5) M. A. Stevens, D. J. Magrath, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 2755 (1958).

(6) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J. All melting points are uncorrected.

formamidine acetate in 500 ml. of ethanol was heated under reflux for 20 hr. The product gradually separated from the hot reaction mixture in the form of colorless, fluffy plates. The chilled mixture was filtered to yield 4.0 g. of 7-methyladenine-3-*N*-oxide, while concentration of the filtrate yielded an additional 1.5 g.; total yield, 5.5 g. (92%). Recrystallization from ethanol yielded colorless needles, m.p. 278° dec. The product was extremely hygroscopic and was rapidly converted to a monohydrate upon exposure to air.

Anal. Calcd. for $C_6H_7N_5O \cdot H_2O$: C, 39.3; H, 4.95; N, 38.2. Found: C, 39.0; H, 4.8; N, 38.3.

Careful drying just prior to analysis resulted in the loss of 10.1% of the weight of the monohydrate (calculated loss: 9.9%):

Anal. Calcd. for $C_6H_7N_5O$: C, 43.6; H, 4.3; N, 42.4. Found: C, 43.7; H, 4.2; N, 42.5.

$\lambda_{max}^{0.1N NaOH}$ 229, 296 μ ; $\log \epsilon$ 4.23, 4.07
 $\lambda_{max}^{0.1N HCl}$ 224.5, 278 μ ; $\log \epsilon$ 4.06, 4.12

Reduction of 7-Methyladenine-3-N-oxide to 7-Methyladenine (V). A solution of 1.0 g. of 7-methyladenine-3-*N*-oxide in 80 ml. of water containing 1 ml. of concentrated ammonium hydroxide was hydrogenated in the presence of 1 g. of freshly prepared Raney nickel catalyst (wet with ethanol) at 3 atmospheres pressure and at room temperature for 20 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. Recrystallization of the residue from aqueous ethanol yielded 0.85 g. of 7-methyladenine, m.p. 345°, identical in every respect with an authentic sample.³

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Effect of Sodium in the Preparation of *n*-Butyllithium

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n-Butyllithium is routinely prepared in this laboratory from 1-bromobutane and lithium metal in diethyl ether by the method of Gilman *et al.*,¹ in yields of 80–95%. Recently metallic lithium of higher grade was made commercially available² so it was of interest to determine the effect of this metal on the yield of *n*-butyllithium. According to information supplied by the manufacturer, the main difference between this new lithium metal and the regular grade lithium is the sodium content, which is approximately 0.005% for the new metal compared to 0.05% for the regular grade metal. By following the usual procedure¹ we obtained a

maximum yield of only 48% with the "low sodium" lithium compared to 80–95% for the regular grade lithium. Moreover the reaction differs in that a precipitate forms during the reaction, the lithium does not become shiny but turns a dull brownish color, and the temperature fluctuates and is difficult to control.

Reaction conditions have been varied in order to improve the yield. Small pieces of sodium were added with no significant result. The temperature was varied from the usual -30 to -40° to the reflux temperature of the ether. Somewhat better yields were obtained at the higher temperatures with a maximum of 59% at 10° . Special stirrers were designed in an effort to minimize the coating of the lithium, but these were unsuccessful. An increase in addition time of 1-bromobutane from the usual 30 min. to 3 hr. at -35° resulted in a yield of 29%. However, the use of half "low sodium" lithium and half regular grade lithium using routine procedures increased the yield to 76%. In another experiment some of the "low sodium" lithium was melted under oil and approximately 0.1% sodium was added. This metal also gave *n*-butyllithium in 76% yield. "Low sodium" lithium³ to which 0.8% sodium was added resulted in an 84.2% yield of *n*-butyllithium by conventional procedures.

In the literature are reports of good yields of *n*-butyllithium from 1-chlorobutane and lithium metal in benzene.⁴ This reaction was attempted in the conventional way with regular grade lithium metal and resulted in low yields of *n*-butyllithium (32–57%). Since the lithium appeared to be heavily coated, more vigorous stirring was used but this did not improve the yield even though the metal was finely dispersed by the stirrer. The use of a lithium dispersion also did not improve the yield. However, when "low sodium" lithium to which 0.8% sodium was added was used, the yields by the conventional method were increased to 70–80%.

In *n*-heptane "low sodium" lithium and 1-chlorobutane resulted in yields from 71.9–73.7%. Regular lithium gave yields from 64–69.6%, but again "low sodium" lithium, to which 0.8% sodium was added,³ gave higher yields of 79.2–81.3% by conventional methods.

Apparently the amount of sodium in the lithium metal appreciably affects the yield of *n*-butyllithium⁵ from *n*-butyl halides and lithium metal, though the reason for this effect is not clear. The

(3) This sample of lithium was kindly provided by the Lithium Corp. of America.

(4) K. Ziegler and H. Colonius, *Ann.*, **479**, 135 (1930); H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, **54**, 1957 (1932); G. Wittig, *Angew. Chem.*, **53**, 241 (1940).

(5) Recently "sodium free" lithium was found to be unreactive toward *t*-butyl chloride. However, lithium containing 1–2% sodium gave good yields of *t*-butyllithium. See M. Stiles and R. P. Mayer, *J. Am. Chem. Soc.*, **81**, 1497 (1959).

(1) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

(2) Available from the Lithium Corp. of America, Inc., Rand Tower, Minneapolis 2, Minn.