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STUDIES IN PURINE CHEMISTRY. VI. A CONVENIENT ONE-STEP SYNTHESIS OF HYPOXANTHINE[1,2]

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EXISTING methods for the preparation of hypoxanthine fall into three categories: (i) cyclization of 4-hydroxy-5, 6-diaminopyrimidine with one-carbon reagents such as formamide and/or formic acid[3,4] or ethyl orthoformate,[5] and treatment of 4-chloro-5, 6-diaminopyrimidine with formamide,[6] (ii) cyclization of 4-aminoimidazole-5-carboxamide with similar one-carbon reagents,[7,8] and base-catalysed cyclization of

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[1] For the previous paper in this series, see E. C. Taylor and C. C. Cheng, J. Org. Chem. In press.

[2] This investigation was supported in part by a grant (C-2551) to Princeton University from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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4-formylaminoimidazole-5-carboxamide,[7] and (iii) modifications of preformed purines, such as desulfurization of 2-mercaptohypoxanthine,[3,9] hydrolysis of adenine,[4,10] 6-cyanopurine,[11] 6-chloropurine[12] and 6-alkylmercaptopurines,[13] and treatment of xanthine with formamide.[14,15] A recently described synthesis of hypoxanthine by the reaction of ethyl orthoformate with aminomalonamidamidine dihydrochloride falls into category (ii), since it has been shown that 4-ethoxymethyleneaminoimidazole-5-carboxamide is initially formed.[8]

We have now found that hypoxanthine may conveniently be prepared in 75 per cent yield in a single step from the commercially available aliphatic intermediate, ethyl acetamidocyanoacetate, by heating with a mixture of ethyl orthoformate, ammonium acetate and alcoholic ammonia.[16] The rationale

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[16] Ethyl acetamidocyanoacetate has recently been utilized (D. S. Acker and J. E. Castle, J. Org. Chem. 23, 2010 (1958) as an intermediate for a convenient two-step synthesis of various 2-substituted hypoxanthines, but hypoxanthine itself is apparently not available by this method.

for this synthesis rests upon a recent discovery in this laboratory[17] that formamidine acetate may be prepared in high yield by heating ethyl orthoformate with ammonium acetate and alcoholic ammonia. Ethyl acetamidocyanoacetate would be converted to its amide and its acetyl grouping removed under the reactions conditions employed, and it is known[18] that aminocyanoacetamide reacts with formamidine to give 4-aminoimidazole-5-carboxamide. The conversion of the latter compound to hypoxanthine with ethyl orthoformate has already been demonstrated.[8]

Experimental

Hypoxanthine. A mixture of 2.5 g of ethyl acetamidocyanoacetate, 2.5 g of ammonium acetate, 10 ml of ethyl orthoformate and 15 ml of a 20% ethanolic ammonia solution was heated in a steel bomb at 180° for 8 hr. The dark brown residue was filtered from the reaction mixture and recrystallized from boiling water (with the use of charcoal) to give 1.5 g (75%) of a light tan solid, m.p. $>360^{\circ}$. The product was identified as pure hypoxanthine by comparison with an authentic sample by paper chromatography and by examination of infrared and ultraviolet absorption spectra.

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