[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Studies in Purine Chemistry. VIII. A Convenient Synthesis of Hypoxanthines and Adenines[1,2]

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The reaction of aminomalonamidamidine (I) dihydrochloride with ortho esters in dimethylformamide yields 2,8-disubstituted hypoxanthines *via* the intermediate formation of 2-alkyl(or aryl)-4-(alkyl(or aryl)ethoxymethylene)-aminoimidazole-5-carboxamides. Hydrolysis of the latter compounds, or reaction of I with one mole of ortho ester, yields 2-substituted 4-aminoimidazole-5-carboxamides from which unsymmetrical 2,8-disubstituted hypoxanthines can be prepared by further reaction with a second ortho ester. The reaction of I with ethyl orthoformate yields hypoxanthine itself in 85% yield in 3–5 minutes. Similarly, the reaction of aminomalondiamidine (XV) dihydrochloride with ortho esters in dimethylformamide yields 2,8-disubstituted adenines. Adenine itself is prepared in 76% yield by the reaction of XV with ethyl orthoformate.

The synthesis of a bicyclic condensed heterocyclic ring system usually involves the initial preparation of one ring followed by closure of the second ring in the terminal stages of the synthesis. The choice of which of the two rings is prepared first is generally dictated by its relative ease of preparation. Thus, in the case of the purines, most known derivatives have been prepared by cyclization with appropriate one-carbon reagents of 4,5-diaminopyrimidine intermediates. The alternative route to purines *via* ring closure of appropriately substituted imidazoles has been much less widely applied because of the relatively inaccessibility of the requisite intermediates.[3]

An attractive route to purines utilizing this second approach (*via* imidazoles) was described several years ago by Shaw.[4] Thus, reduction of phenylazomalonamidamidine with zinc and formic acid to formylaminomalonamidamidine, followed by cyclization to 4-aminoimidazole-5-carboxamide and closure of the pyrimidine ring with formamide and urea yielded hypoxanthine and xanthine, respectively. Hypoxanthine was also prepared directly from formylaminomalonamidamidine by reaction with formamide. Similarly, reduction of phenylazomalondiamidine with zinc and formic acid to formylaminomalondiamidine, followed by cyclization to 4-aminoimidazole-5-carboxamidine, formylation with formic acid and acetic anhydride and cyclization with potassium bicarbonate, afforded adenine.

However, since the intermediates aminomalonamidamidine (I) and aminomalondiamidine (XV) constitute the entire skeletal backbone of the hypoxanthine and adenine systems, respectively, it appeared that a one-step purine synthesis from these aliphatic intermediates might be possible in which the missing C_2 and C_8 atoms could be supplied simultaneously by means of a single one-carbon reagent. The present paper describes a convenient purine synthesis from the intermediates I and XV which utilizes ortho esters as cyclization reagents.[5]

The reaction of aminomalonamidamidine (I) hydrochloride with an excess of ethyl orthoformate in dimethylformamide as solvent gave chromatographically pure hypoxanthine (II) in 85% yield in 3–5 minutes. The use of acetonitrile as solvent was likewise successful, but its lower boiling point necessitated a longer reaction time. Although spectroscopic evidence for the formation of a monocyclic intermediate was obtained, it proved to be impossible to isolate and identify it under the above reaction conditions, for further cyclization to hypoxanthine took place with great ease. However, the use of one molar equivalent of ethyl orthoformate in dimethylformamide solution led in 74% yield to 4-aminoimidazole-5-carboxamide (VIII) hydrochloride. Subsequent reaction with ethyl orthoformate gave hypoxanthine in quantitative yield. The formation of VIII by the above reaction is thus consistent with the recently described synthesis of VIII from phenylazomalonamidamidine by reduction in the presence of formic acid to formylaminomalonamidamidine, followed by cyclization to 4-formylaminoimidazole-5-carboxamide and subsequent hydrolysis.[6]

The reaction of aminomalonamidamidine (I) with an excess of ethyl orthoacetate in dimethylformamide solution proceeded more slowly and yielded 2-methyl-4-(methylethoxymethylene)-aminoimidazole-5-carboxamide (XI) as an initial product after 15 minutes, and 2,8-dimethylhypoxanthine (III) after 20 hours. Vacuum sublimation of XI gave III in quantitative yield. Advantage may be taken of the slower rate of reaction of higher ortho esters with aminomalonamidamidine (I) to prepare imidazole intermediates which upon subsequent reaction with a second ortho ester yield unsymmetrically substituted hypoxanthines. Thus, 2-methyl-4-aminoimidazole-5-carboxamide (IX) was prepared either by reaction of I with one mole of ethyl orthoacetate in dimethylformamide, or by hydrolysis of 2-methyl-4-(methylethoxymethylene)-aminoimidazole-5-carboxamide (XI). Subsequent cyclization with ethyl orthoformate yielded 8-methylhypoxanthine (IV). In a similar fashion, 2-methylhypoxanthine (V) was prepared by vacuum

(1) For the previous paper in this series, see E. C. Taylor and C. C. Cheng, *J. Org. Chem.*, **25**, 148 (1960).

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(3) For a recent review of purine chemistry, see A. Bendich in "The Nucleic Acids, Chemistry and Biology," ed. by E. Chargaff and J. N. Davidson, Academic Press, Inc., New York, N. Y., 1955, p. 81.

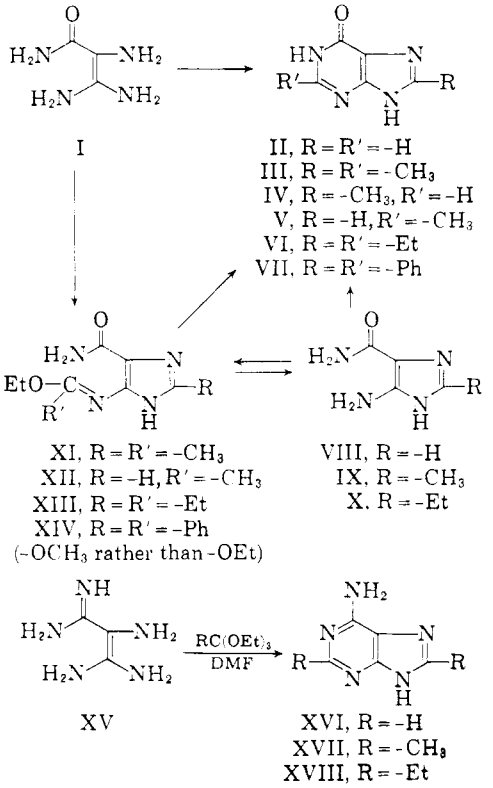
(4) E. Shaw, *J. Biol. Chem.*, **185**, 439 (1950).

(5) A preliminary communication describing the synthesis of hypoxanthine by this method has been published: E. Richter and E. C. Taylor, *Angew. Chem.*, **67**, 303 (1955). A brief discussion of the present work has also been given by E. C. Taylor, T. S. Osdene, E. Richter and O. Vogl in "The Chemistry and Biology of Purines," ed. by G. E. W. Wolstenholme and C. M. O'Connor, J. and A. Churchill Ltd., London, 1957, p. 20.

(6) J. A. Montgomery, K. Hewson, R. F. Struck and Y. F. Shealy, *J. Org. Chem.*, **24**, 256 (1959).

sublimation of 4-(methylethoxymethylene)-aminoimidazole-5-carboxamide (XII), which was obtained by the reaction of VIII with ethyl orthoacetate.

Other ortho esters reacted similarly with aminomalonamidamidine (I). Ethyl orthopropionate yielded 2-ethyl-4-aminoimidazole-5-carboxamide (X) after acid hydrolysis of the initially formed 4-(ethylethoxymethylene)-amino derivative XIII, and further reaction with ethyl orthopropionate gave 2,8-diethylhypoxanthine (VI). This latter



purine could be prepared directly from I, but a long reaction time (60 hours) was necessary because of the reduced activity of the ortho ester. Reaction of I with methyl orthobenzoate gave 2-phenyl-4-(phenylmethoxymethylene)-aminoimidazole-5-carboxamide (XIV) which upon vacuum sublimation gave 2,8-diphenylhypoxanthine (VII).

Adenine derivatives were similarly prepared by the reaction of ortho esters with aminomalondiamidine (XV) dihydrochloride. Thus, the reaction of XV with ethyl orthoformate in dimethylformamide gave adenine (XVI) in 72% yield. Attempts to isolate 4-aminoimidazole-5-carboxamidine from this reaction were unsuccessful; even with one mole of ortho ester and a very short reaction time, only adenine and unreacted XV could be isolated. The reaction of XV with ethyl orthoacetate in dimethylformamide gave 2,8-dimethyladenine (XVII) and the use of ethyl orthopropionate similarly gave 2,8-diethyladenine (XVIIII).

Hypoxanthine may be prepared from ethyl cyanoacetate in 48% over-all yield in six steps by a modification[1] of the classical Traube synthesis, and in 75% yield *in one step* from commercially available ethyl acetamidocyanoacetate.[7] Although the present method provides a convenient route to a variety of 2,8-disubstituted hypoxanthines, the over-all yield of hypoxanthine itself from ethyl cyanoacetate is only 36%, and the method thus compares unfavorably with other available procedures for the synthesis of the parent compound. Adenine may be prepared in 33% over-all yield by the classical Traube route from malononitrile, and also in 33% yield in the same number of steps by the present method. The latter has additional synthetic applicability, however, for a variety of 2,8-disubstituted adenine derivatives may conveniently be made in a single terminal step from the common aliphatic precursor, aminomalondiamidine (XV).

Experimental[8,9]

4-Aminoimidazole-5-carboxamide (VIII) Hydrochloride.—A mixture of 5.7 g. of aminomalonamidamidine dihydrochloride,[10] 5 ml. of ethyl orthoformate, 25 ml. of dimethylformamide and 15 ml. of 2 *N* sodium methoxide in methanol was heated under reflux for 5 minutes. The product separated on cooling and was collected by filtration; yield 3.9 g. An additional 0.9 g. was obtained by dilution of the mother liquor with ethanol and water. Recrystallization from ethanol then gave 3.6 g. (74%) of 4-aminoimidazole-5-carboxamide hydrochloride, m.p. 255–256°, identical in every respect with an authentic sample.[10]

Hypoxanthine (II).—A mixture of 2 g. of aminomalonamidamidine dihydrochloride, 10 ml. of ethyl orthoformate and 20 ml. of dimethylformamide was heated under reflux for 3–5 minutes (until the initially clear solution turned turbid). The mixture was cooled, filtered and the collected solid recrystallized from ethanol to give 1.31 g. (85%) of colorless hypoxanthine, identical in every respect with an authentic sample.

2-Methyl-4-(methylethoxymethylene)-aminoimidazole-5-carboxamide (XI). Method A.—A mixture of 5 g. of aminomalonamidamidine dihydrochloride, 25 ml. of ethyl orthoacetate and 50 ml. of dimethylformamide was heated under reflux for 15 minutes and cooled. The white precipitate which separated was collected by filtration and recrystallized from 70% aqueous ethanol to give 4.1 g. (74%), m.p. 224–225°.

Method B.—A mixture of 9.4 g. of aminomalonamidamidine dihydrochloride (well dried over potassium hydroxide), 40 ml. of acetic anhydride and 50 ml. of ethyl orthoformate was heated under reflux for 6 hours. A clear solution was obtained after 2 hours. The mixture was evaporated to a small volume under reduced pressure, 50 ml. of absolute ethanol added, and the mixture was again evaporated to a small volume. This process was repeated, and the residue was then collected by filtration; yield 6.05 g., m.p. 217°. An additional 1.01 g. was obtained by concentration of the mother liquor; total yield 7.06 g. (67%). Recrystallization from ethanol raised the melting point to 224°.

Anal. Calcd. for $C_9H_{14}N_4O_2$: C, 51.4; H, 6.7; N, 26.65. Found: C, 51.7; H, 6.6; N, 26.3.

2-Methyl-4-aminoimidazole-5-carboxamide (IX) Hydrochloride. Method A.—Fifteen grams of 2-methyl-4-(methylethoxymethylene)-aminoimidazole-5-carboxamide was added to 60 ml. of 25% hydrochloric acid. When the initial exothermic reaction had subsided, the mixture was brought to boiling and then cooled. Filtration yielded 11.0 g. (87%) of colorless crystals, m.p. 258–259°, which were recrystallized from aqueous ethanol.

Method B.—A mixture of 3.78 g. of aminomalonamidamidine dihydrochloride, 3.9 ml. of triethylorthoacetate, 100 ml. of ethanol and 1.08 g. of sodium methoxide was heated under reflux for 20 minutes, cooled and 50 ml. of ether added. The solid which precipitated was collected by filtration and recrystallized from aqueous ethanol; yield 1.9 g. (54%), m.p. 258–259°.

(7) E. C. Taylor and C. C. Cheng, *Tetrahedron Letters*, No. 12, 9 (1959).

(8) All melting points are uncorrected.

(9) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J.

(10) E. Shaw and D. W. Woolley, *J. Biol. chem.*, **181**, 89 (1949).

Anal. Calcd. for $C_6H_8N_4O \cdot HCl$: C, 34.0; H, 5.1; N, 31.7. Found: C, 34.5; H, 5.1; N, 31.75.

8-Methylhypoxanthine (IV).[11-13]—A mixture of 1.1 g. of 2-methyl-4-aminoimidazole-5-carboxamide hydrochloride, 7 ml. of ethyl orthoformate and 20 ml. of dimethylformamide was heated under reflux for 5 minutes, cooled and filtered to give 0.9 g. (96%) of colorless crystals, m.p. >380°. The reported melting point for this compound is >300°.[11] The product was recrystallized from dilute hydrochloric acid for analysis.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.0; N, 37.3. Found: C, 48.1; H, 4.2; N, 37.9.

4-(Methylethoxymethylene)-aminoimidazole-5-carboxamide (XII).—A mixture of 3.24 g. of 4-aminoimidazole-5-carboxamide hydrochloride, 6 ml. of ethyl orthoformate and 20 ml. of dimethylformamide was heated under reflux for 2 minutes and then cooled. Filtration gave a colorless solid which was recrystallized from aqueous ethanol; yield 2.5 g. (64%), m.p. 248°, followed by resolidification.

Anal. Calcd. for $C_8H_{12}N_4O_2$: C, 49.0; H, 6.2. Found: C, 49.0; H, 6.1.

2-Methylhypoxanthine (V).[14,15]—Two grams of 4-(methylethoxymethylene)-aminoimidazole-5-carboxamide was heated above its melting point for 30 minutes and the resolidified melt recrystallized from water to give 1.48 g. (97%) of 2-methylhypoxanthine, identical in all respects with an authentic sample.[14]

2,8-Dimethylhypoxanthine (III).[16-18] **Method A.**—Vacuum sublimation (250° (0.05 mm.)) of 2-methyl-4-(methylethoxymethylene)-aminoimidazole-5-carboxamide gave 2,8-dimethylhypoxanthine in quantitative yield as a colorless sublimate, m.p. 365° dec.

Method B.—A mixture of 10 g. of aminomalonamidamidine dihydrochloride, 50 ml. of ethyl orthoacetate and 50 ml. of dimethylformamide was heated under reflux for 10 hours. The hot reaction mixture was treated with charcoal and filtered. Concentration of the filtrate to a small volume and addition of ethanol resulted in the separation of a colorless solid which was collected by filtration, dried and sublimed at 250° (0.05 mm.) to give 6.8 g. (78%) of 2,8-dimethylhypoxanthine, m.p. 365° dec. This compound is reported to melt at 335°[16] and above 300°.[18]

Anal. Calcd. for $C_7H_8N_4O$: C, 51.2; H, 4.9; N, 34.1. Found: C, 51.0; H, 4.75; N, 34.5.

2-Ethyl-4-aminoimidazole-5-carboxamide (X) Hydrochloride.—A mixture of 10 g. of aminomalonamidamidine dihydrochloride, 50 ml. of ethyl orthopropionate and 20 ml. of dimethylformamide was heated under reflux for 3.5 hours and then concentrated under vacuum to a small volume. The residue was treated with a mixture of 50 ml. of ethanol and 15 ml. of 50% hydrochloric acid, followed by 75 ml. of ether. The white solid which separated was collected by filtration; yield 7 g. (70%), m.p. 256–257°.

Anal. Calcd. for $C_6H_{10}N_4O \cdot HCl$: C, 37.8; H, 5.8; N, 29.4. Found: C, 38.3; H, 6.0; N, 29.5.

2,8-Diethylhypoxanthine (VI).—A mixture of 10 g. of aminomalonamidamidine dihydrochloride, 50 ml. of ethyl orthopropionate and 50 ml. of dimethylformamide was heated under reflux for 60 hours, filtered and concentrated to a small volume under reduced pressure. Addition of ethanol and ether precipitated a colorless solid (6.4 g., 60%), m.p. 282° dec., which was purified by recrystallization from aqueous ethanol.

Anal. Calcd. for $C_9H_{12}N_4O \cdot {}^1/_2H_2O$: C, 54.0; H, 6.5; N, 28.0. Found: C, 54.2; H, 6.8; N, 27.8.

The water of recrystallization was removed by vacuum sublimation.

Anal. Calcd. for $C_9H_{12}N_4O$: C, 56.2; H, 6.3; N, 29.15. Found: C, 56.0; H, 6.4; N, 29.1.

2-Phenyl-4-(phenylmethoxymethylene)-aminoimidazole-5-carboxamide (XIV).—A mixture of 2.5 g. of aminomalonamidamidine dihydrochloride, 12 ml. of trimethyl orthobenzoate and 10 ml. of dimethylformamide was heated under reflux for 20 minutes. The resulting red solution was concentrated under reduced pressure and the residue was dissolved in ethanol. Addition of water caused the separation of 2.5 g. (58%) of red crystals which were recrystallized from ethanol–benzene, followed by recrystallization from aqueous ethanol; m.p. 155–160° with immediate resolidification.

Anal. Calcd. for $C_{18}H_{16}N_4O_2 \cdot {}^1/_2H_2O$: C, 65.65; H, 4.8; N, 17.0. Found: C, 65.2; H, 4.9; N, 17.5.

2,8-Diphenylhypoxanthine (VII).—Vacuum sublimation of 2-phenyl-4-(phenylmethoxymethylene)-aminoimidazole-5-carboxamide at 250° (0.15 mm.) yielded 2,8-diphenylhypoxanthine in 70% yield. The product was recrystallized from aqueous ethanol to give colorless crystals, m.p. 380°.

Anal. Calcd. for $C_{17}H_{12}N_4O$: C, 70.8; H, 4.2; N, 19.4. Found: C, 70.8; H, 4.1; N, 19.2.

Adenine (XVI).—A mixture of 2 g. of aminomalondiamidine dihydrochloride, 10 ml. of ethyl orthoformate and 20 ml. of dimethylformamide was heated under reflux for 15 minutes and then evaporated to dryness under reduced pressure. The residue was dissolved in 50 ml. of 1 *N* hydrochloric acid, treated with charcoal and filtered. Addition of ammonium hydroxide to the filtrate (to *p*H 8), followed by concentration to about 15 ml. and cooling caused the separation of 1.0 g. (72%) of colorless adenine, m.p. 361° dec., identical in every respect with an authentic sample.

The use of acetonitrile as solvent in this reaction gave adenine in 65% yield.

2,8-Dimethyladenine (XVII).—A mixture of 3 g. of aminomalondiamidine dihydrochloride, 10 ml. of ethyl orthoacetate and 10 ml. of dimethylformamide was heated under reflux for 15 minutes and then concentrated to about half its volume under reduced pressure. Cooling and filtering gave 1.5 g. (47%) of a tan solid which was recrystallized from aqueous ethanol with the addition of ether; m.p. 310–320° dec.

Anal. Calcd. for $C_7H_9N_5 \cdot HCl$: C, 42.2; H, 5.0; N, 35.1. Found: C, 41.9; H, 4.9; N, 35.8.

Treatment of an aqueous solution of the hydrochloride with ammonium hydroxide precipitated the free base which was purified by vacuum sublimation to give colorless crystals, m.p. 342° dec.

Anal. Calcd. for $C_7H_9N_5$: C, 51.5; H, 5.6; N, 42.9. Found: C, 51.45; H, 5.6; N, 42.8.

2,8-Diethyladenine (XVIII).—A mixture of 7 g. of aminomalondiamidine dihydrochloride, 40 ml. of ethyl orthopropionate and 30 ml. of dimethylformamide was heated under reflux for 3 hours and then evaporated nearly to dryness under reduced pressure. The residue was dissolved in 2 *N* hydrochloric acid, and the resulting solution was treated with charcoal and filtered. Concentration of the filtrate to a small volume followed by addition of ethanol and ether resulted in the separation of 3 g. (35%) of 2,8-diethyladenine hydrochloride. The free base was prepared in the form of colorless needles, m.p. 242°, by dissolving the hydrochloride salt in water and adding ammonium hydroxide. The product was purified readily by vacuum sublimation.

Anal. Calcd. for $C_9H_{13}N_5$: C, 56.5; H, 6.85; N, 36.6. Found: C, 56.4; H, 6.5; N, 36.6.

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