corresponding urea Va–c (*cf.* Experimental Section) by acid-catalyzed hydration. Compound IIIf gave, on pyrolysis, the N-sulfonylcarbodiimide IVf, a class of compounds until recently not described in literature,[8] and this (IVf) in turn yielded the N-sulfonylurea Vc (*cf.* Experimental Section) on hydration.

Experimental Section[9]

4,5-Diphenyl-1-oxo-1,2,3,5-thiaoxadiazole (IIIa).—A solution of benzhydroxamoyl chloride (7.8 g., 0.05 mole) in ether (250 ml.) was extracted with a cold 4% aqueous solution of sodium hydroxide (50 g., equivalent to 0.05 mole of NaOH) in a separatory funnel and the ether layer containing benzonitrile oxide was then removed, washed with a small quantity of water, dried over anhydrous calcium chloride for about 2 min., and treated with N-sulfinylaniline[3] (7.0 g., 0.05 mole) with agitation. A vigorous exothermic reaction developed almost immediately at the end of which the clear reaction mixture was set aside for about 2 hr. at room temperature. Removal of the solvent under diminished pressure afforded an oily product which was treated with a small quantity of methanol and left in the refrigerator overnight. The solid that had separated was filtered, washed with a little ice-cold methanol, air-dried, and recrystallized from a mixture of benzene and *n*-hexane, m.p. 72–73°, yield 8.5 g.

With the exception of IIIf, all the compounds listed in Table I were prepared by an essentially similar procedure.

4-(4-Chlorophenyl)-5-(4-methylbenzenesulfonyl)-1-oxo-1,2,3,-5-thiaoxadiazole (IIIf).—Anhydrous triethylamine (5.1 g., 0.05 mole) was added in one portion to an ice-cooled and well-stirred solution of 4-chlorobenzhydroxamoyl chloride (9.5 g., 0.05 mole) in absolute ether (250 ml.) and, after a few minutes, the precipitate of triethylamine hydrochloride was filtered rapidly and washed with a small quantity of absolute ether. The combined filtrates were stirred and, with the exclusion of moisture, treated immediately with N-sulfinyl-4-methylbenzenesulfonamide[3] (10.9 g., 0.05 mole) added in one lot. The reaction mixture, protected from moisture, was then set aside for about 2 hr. at room temperature, filtered to remove a small quantity of precipitate, and stripped of solvent under diminished pressure. The residue was recrystallized from *n*-hexane, m.p. 89–90° dec., yield 8.5 g.

General Procedure for the Preparation of the Carbodiimides IVa–h (Table II).—The pyrolyses of the 1-oxo-1,2,3,5-thiaoxadiazoles IIIa–h were carried out in a temperature-controlled and electrically heated oil bath. The compounds were taken in small pear-shaped distillation flasks with standard joints and, with the exclusion of moisture and under a slow stream of dry nitrogen, heated to their melting points at which temperature most of these decomposed, spontaneously splitting off sulfur dioxide. In some cases, the temperature had to be raised to a little beyond the melting points until vigorous evolution of sulfur dioxide set in. The temperature was maintained steady until the decomposition was complete and the oily product was then cooled to room temperature. Some of the carbodiimides solidified and were recrystallized from suitable solvents, and the others were distilled under vacuum and obtained as liquids (Table II). All of these compounds exhibited intense absorption in the 4.5–5.0-μ region of the infrared which is characteristic of carbodiimides.

The ureas mentioned below were obtained by treating the corresponding carbodiimides with 2 *N* hydrochloric acid.

N-(4-Chlorophenyl)-N′-(4-methoxyphenyl)urea (Va) was recrystallized from ethanol, m.p. 265–267°. The melting point on admixture with an authentic specimen (prepared by treating 4-methoxyaniline with 4-chlorophenylisocyanate) was undepressed.

N-(4-Chlorophenyl)-N′-(4-methylphenyl)urea (Vb) was recrystallized from ethanol, m.p. 298–300°.

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.02; N, 10.75. Found: C, 64.82; H, 5.24; N, 10.81.

N-(4-Chlorophenyl)-N′-(4-methylbenzenesulfonyl)urea (Vc) was recrystallized from a mixture of benzene and *n*-hexane, m.p. 170–172°.

Anal. Calcd. for $C_{14}H_{13}ClN_2O_3S$: C, 51.78; H, 4.03; N, 8.63. Found: C, 51.82; H, 4.29; N, 8.52.

Acknowledgment.—The authors would like to thank Professor T. R. Govindachari for his interest in this work and Dr. S. Selvavinayakam and his staff for elemental analyses and spectra.

(8) H. Ulrich and A. A. R. Sayigh, *Angew. Chem. Intern. Ed. Engl.*, **3**, 639 (1964); R. Neidlein and E. Heukelbach, *Tetrahedron Letters*, 149 (1965).

(9) Melting points are uncorrected.

Observations on the Cyclization of a Substituted α-Formamidoamidine to Aminoimidazolecarboxamide Derivatives[1]

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The cyclization of α-formamido-N-benzylguanylacetamide (I) could be influenced by reaction conditions to yield either a ring benzyl- (II) or benzylaminoimidazole (III) as the major product. These were converted to 9-benzyl- and 3-benzylhypoxanthine, respectively.

The discovery of aminoimidazolecarboxamide derivatives as intermediates in the biosynthesis of purines[2] prompted the development of new syntheses for aminoimidazoles. Among these was the cyclization of α-formamidoamidines which provided a useful route,[3] one which was subsequently shown[4] to be the natural ring-closing step. In chemical work directed toward the possible application of this cyclization toward the synthesis of imidazole nucleosides and nucleotides, it was of interest to determine to what extent ring closure could be influenced to take place to an N-alkylamidine nitrogen since this would lead to substitution on the imidazole ring in the position characteristic of the natural derivatives as in II. The alternative product would, of course, be the alkylaminoimidazole (III).

In the work described a benzyl group served as a model substituent. The monosubstituted amidine (I, R = C_7H_7) was synthesized from cyanoacetamide by treatment of the imino ethyl ether with 1 equiv. of benzylamine; N-benzylguanylacetamide thus produced yielded the formamido derivative (I) on coupling with benzenediazonium chloride and reductive formylation. It was characterized as the formate salt.

(1) Support of the U. S. Public Health Service (through CA-05294 and GM-1240) is gratefully acknowledged.

(2) W. Shive, W. Ackerman, M. Gordon, M. E. Getzendaner, and R. E. Eakin, *J. Am. Chem. Soc.*, **69**, 725 (1947).

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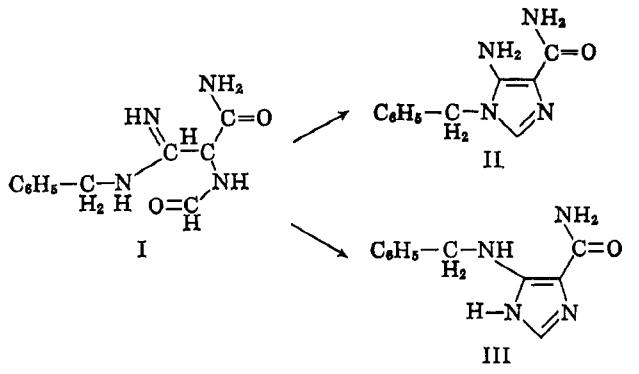
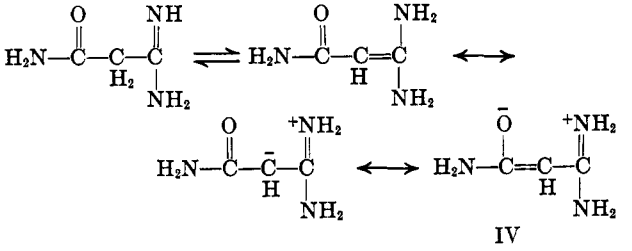
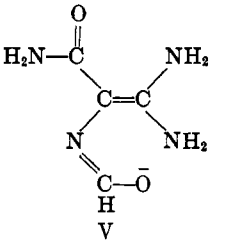


Imidazole formation from I was studied under a number of conditions. The proportions of the isomers produced (II and III) was readily determined by a convenient separation of the isomers based on the solubility of III, but not II, in aqueous alkali. This property was the basis of assigning the structures to the isomers since the ring hydrogen in aminoimidazolecarboxamide is mildly acidic.[5] As expected, the benzylamino derivative (III) was the product obtainable in highest yields, for example, 60% in refluxing acetonitrile. However, the direction of ring closure could be influenced by reaction conditions to produce the ring benzyl isomer II as the major product, although in lower yield (39%), by refluxing in methanolic sodium methylate. In this case only about 6% of III was formed. The variations encountered probably reflect, among other things, different cyclizing species which could include not only the protonated form of I and the free base but also tautomeric structures derived from the latter. Malonamamidine, in alkaline solution, has an absorption maximum at 270 mμ, although in acid solution it is transparent to ultraviolet light. This is apparently due to stabilization of the free base as in IV. In formamidomalonam-



amidines (and other acylamido derivatives), this pH-dependent spectral behavior is also found generally at a much lower pH, indicating considerable stabilization of the base through participation of the acylamido group. This may involve another proton loss as in V, a structure supported by the occurrence of a pH-dependent absorption maximum at the same wave length as that of the imidazole derivable on cyclization. Some observations of this phenomenon are described below. Although this behavior of malonamamidines has not been systematically studied, it seems likely that the course of the cyclization of I is related to these properties.

Ring-substituted imidazoles of type III of interest in purine biosynthesis are ribosides and have become available to a limited extent by various methods.[6] The observations reported here are of value in increasing the flexibility of synthetic approaches not only to the imidazoles but also to derivable purines,[7] particularly those substituted in the 3 position, recently encountered in nature with greater frequency.[8] To demonstrate the possible use of II and III in purine synthesis, their conversion to 9-benzylhypoxanthine and 3-benzylhypoxanthine was carried out by heating with formamide or formic acid, respectively.



Experimental Section[9]

N-Benzylguanylacetamide Hydrochloride.—Cyanoacetamide (15 g.) in dioxane (750 ml.), anhydrous ether (50 ml.), and ethanol (10 ml.) was cooled in an ice bath and treated with a stream of hydrogen chloride in the usual way, then left overnight at 4°. The separated crystals were filtered, washed with dry ether, and desiccated *in vacuo* over sodium hydroxide pellets. The imino ether hydrochloride was obtained as needles, 17 g., 57%, m.p. 112–113° dec., and was used shortly after preparation without further treatment.

The imino ether hydrochloride (3.0 g.), when added to ethanol containing benzylamine (1.9 ml. of base in 20 ml.), dissolved with the evolution of heat. A new crystalline precipitate formed which was collected after 2 days and washed with an ethanol–ether mixture yielding 2.5 g., m.p. 152–154°, 61%. Recrystallization from alcohol gave m.p. 158–160°.

Anal. Calcd. for $C_{10}H_{14}ClN_3O$: Cl^-, 15.6; N, 18.46. Found: Cl^-, 15.6; N, 18.33.

Phenylazo-N-benzylguanylacetamide.—N-Benzylguanylacetamide hydrochloride (5.3 g.) in water (25 ml.) was treated with a solution of benzenediazonium chloride prepared from aniline (2.2 ml.) in 6 *N* HCl (14 ml.) and aqueous sodium nitrite (1.84 g. in 12 ml. of water and ice, 10 g.). The addition of concentrated aqueous sodium acetate precipitated the free base of the product. After recrystallization from aqueous alcohol, there was obtained 5.6 g., 80%, m.p. 136–138°.

Anal. Calcd. for $C_{16}H_{17}N_5O$: N, 23.72. Found: N, 23.64.

Formamido-N-benzylguanylacetamide Formate (I).—Phenylazo-N-benzylguanylacetamide hydrochloride (10 g.) in 98% formic acid (75 ml.) was decolorized with zinc dust (6 g.) at room temperature. The filtrate was concentrated *in vacuo* and residual formic acid was driven off by repeated concentrations with added water. An aqueous solution of the residue was treated with hydrogen sulfide and the filtrate from the zinc sulfide was taken to dryness under reduced pressure. The residue crystallized as the formate salt. After thinning with ether for filtration, the product was obtained as colorless needles, 7.6 g., 80%, m.p. 129–130°. A sample recrystallized from alcohol and ether melted at 131–132°.

Anal. Calcd. for $C_{11}H_{14}N_4O_2 \cdot HCO_2H$: C, 51.42; H, 5.75. Found: C, 51.55; H, 5.67.

4(5)-Benzylamino-5(4)-imidazolecarboxamide (III).—The N-benzylamidine formate salt (I, R = C_7H_7, 0.20 g.) was refluxed for 2 hr. in acetonitrile (10 ml.). After removal of the solvent, the residue was stirred with cold 1 *N* NaOH (10 ml.)

(5) A p*K* of 9.2 was observed for the imino hydrogen of 4(5)-amino-5(4)-imidazolecarboxamide by titration in water.

(6) J. Baddiley, J. G. Buchanan, and J. Stewart, *Proc. Chem. Soc.*, 149 (1957); E. Shaw, *J. Am. Chem. Soc.*, **81**, 6021 (1959); **83**, 4770 (1961); G. Shaw and D. V. Wilson, *J. Chem. Soc.*, 1077 (1963), and earlier papers.

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

(8) H. S. Forrest, D. Hatfield, and J. M. Lagowski, *J. Chem. Soc.*, 963 (1961); N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.*, **84**, 2148 (1962).

(9) Microanalyses were performed by S. Theodore Bella of the Rockefeller Institute and Alfred Bernhardt, Mülheim, Germany. Melting points were taken on a copper block and are uncorrected.

which dissolved most of the material. The filtrate was slowly treated with glacial acetic acid to precipitate the product in crystalline form, 0.10 g., 65%, m.p. 159–161°. Recrystallization from aqueous alcohol gave m.p. 165–166°. At pH 6.5, the product exhibited two maxima: at 235 mμ (ε 5700) and at 280–281 mμ (ε 13,300).

Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.11; H, 5.59; N, 25.92. Found: C, 61.32; H, 5.46; N, 25.79.

When the above reaction was carried out with added sodium bicarbonate (one-fourth of the starting material by weight), the yield of III dropped to 38% while the yield of II rose correspondingly to 25% (isolated as the alkali-insoluble fraction, *cf.* below).

1-Benzyl-5-amino-4-imidazolecarboxamide (II).—The N-benzylamidine formate salt (I, R = C_7H_7, 0.60 g.) was refluxed for 4 hr. in methanol (50 ml.) containing sodium methylate (1.9 equiv.). The solution was neutralized with acetic acid and taken to dryness under reduced pressure. The residue was triturated with cold 1 *N* NaOH which provided the product as the crystalline insoluble portion, 0.18 g., 39%, m.p. 235–240°. On recrystallization from aqueous alcohol the amide had m.p. 249–251°. (The alkaline filtrate when brought to pH 4, yielded 6% of the isomeric product III.) At pH 6.5, a single maximum absorption in the ultraviolet was found at 266–267 mμ (ε 12,800).

Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.11; H, 5.59; N, 25.92. Found: C, 61.51; H, 5.58; N, 25.34.

The action of heat alone (15 min. at 155–160°)[9] on the hydrochloride of I gave 15–25% yields of the ring benzyl isomer (II) in a number of runs.

9-Benzylhypoxanthine.—1-Benzyl-5-amino-4-imidazolecarboxamide (110 mg.) was heated in formamide (5 ml.) at 180° for 1.5 hr. Long needles formed on cooling which were collected, dissolved in dilute alkali, and precipitated by acidification to yield 100 mg., m.p. 295–297°.[10]

Anal. Calcd. for $C_{12}H_{10}NO$: C, 63.71; H, 4.46. Found: C, 63.40; H, 4.37.

3-Benzylhypoxanthine.—4 (5)-Benzylamino-5(4)-imidazolecarboxamide (0.40 g.) was refluxed for 30 hr. in 98% formic acid (10 ml.) followed by removal of the formic acid. The residue was stirred with water with addition of aqueous sodium bicarbonate as needed to reach neutrality. The filtered product, 0.3 g., had m.p. 282–283° which remained unaltered on recrystallization from methanol. For 3-benzylhypoxanthine, λ_{max} 255 mμ (ε 9800) was observed in 0.1 *N* HCl and λ_{max} 265 mμ (ε 9400) in 0.1 *N* NaOH.

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 25.05. Found: C, 63.70; H, 4.46; N, 24.77.

When the refluxing was carried out for only 7 hr., considerable uncyclized formyl derivative was obtainable on fractional crystallization. The intermediate obtained has been characterized below.

4(5)-N-Benzylformamido-5(4)-imidazolecarboxamide.—To the benzylamino compound (III, 0.20 g.) in 98% formic acid (1 ml.) was added acetic anhydride (5 ml.), and the solution was held at 70° for 0.5 hr. After complete removal of the reagents, the residue was crystallized from ethyl acetate to yield 0.16 g., m.p. 188–189°.

Anal. Calcd. for $C_{12}H_{12}NO_2$: C, 59.02; H, 4.95; N, 22.9. Found: C, 59.22; H, 4.09; N, 22.3.

Spectral Properties of Malonamamidine, Formamidomalonamamidine, and Carbethoxymalondiamidine.—Malonamamidine hydrochloride[3] in 0.01 *N* NaOH exhibited λ_{max} at 270 mμ (ε 7600), probably a low value due to instability at this pH. The absorption disappeared on acidification. In 0.05 *M* glycine buffer, pH 10, the peak had a low intensity, about 9% of that seen in 0.01 *N* NaOH. In acylamidomalonamamidines, absorption maxima appear at much lower pH values. Dilutions of formamidomalonamamidine hydrochloride[3] were made in a series of phosphate buffers. With increasing pH, a band at 268–270 mμ of increasing intensity was observed reaching a maximum molar extinction coefficient of 20,000 at pH 8.6 and above. It could be estimated that an acid of p*K* about 7.5 was concerned. Below pH 4.5, solutions of the amidine were transparent down to 225 mμ and the absorption observed above that pH completely disappeared on acidification. Near pH 12, the absorption gradually diminished on standing owing to hydrolysis.

Carbethoxyamidomalondiamidine dihydrochloride[11] behaved similarly with a pH-dependent band appearing at 288 mμ (ε 21,700). An estimated p*K* of 5.2 for the acid producing this species on ionization was reached from examination of the absorption at various pH values.

(10) J. A. Montgomery and C. Temple [*J. Am. Chem. Soc.*, **83**, 630 (1961)] gave an alternate synthesis of 9-benzylhypoxanthine.

(11) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **194**, 641 (1952).

Aromatic Substitution. XXIII.[1] Nitration and Nitrosation of Pyridine with Nitronium and Nitrosonium Tetrafluoroborate. Isolation of N-Nitro- and N-Nitrosopyridinium Tetrafluoroborates

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The nitration and nitrosation of pyridine with nitronium and nitrosonium tetrafluoroborate was investigated in nitromethane, acetonitrile, tetramethylene sulfone, and sulfur dioxide solutions. Exclusive N substitution was observed, with no evidence of N → C migration, even at elevated temperatures. The stable crystalline N-nitro- and N-nitrosopyridinium tetrafluoroborates were isolated and their structure was proved through analytical and spectroscopic (infrared and n.m.r.) data. Previously reported direct N nitrations of pyridine must be considered as nitrations of pyridinium salts (formed in the acidic reaction media).

The pyridine nucleus was reported to be resistant to electrophilic nitration, which could be effected only under drastic conditions.

Friedl[3] first reported the nitration of pyridine. He obtained a 15% yield of nitropyridine with potassium nitrate and fuming sulfuric acid at 330°. Other investigators, however, using the same procedure could not obtain more than 1% yield.[4,5]

The use of nitrogen dioxide and aluminum chloride leads to an addition compound of nitrogen dioxide and pyridine.[6] 3-Nitropyridine was reported to be obtained, however, by treatment of pyridine with nitrogen dioxide and carbon dioxide at 115–120°.[7]

(1) Part XXII: G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *J. Am. Chem. Soc.*, **86**, 2203 (1964).

(2) Visiting Professor of Chemistry, The Ohio State University, 1963; to whom correspondence should be addressed at the Department of Chemistry, Western Reserve University, Cleveland, Ohio.

(3) F. Friedl, *Ber.*, **45**, 428 (1912); *Monatsh.*, **34**, 759 (1913).

(4) A. Kirpal and E. Reiter, *Ber.*, **58**, 699 (1925).

(5) H. J. den Hertog, Jr., and J. Overhoff, *Rec. trav. chim.*, **49**, 552 (1930).

(6) A. Schaarschmidt, H. Balzerkiewicz, and J. Gante, *Ber.*, **58**, 499 (1925).

(7) P. Schorigin and A. V. Topchiev, *ibid.*, **69**, 1874 (1936).