# Amidinoacetamides in the Synthesis of Pyrimidines, Imidazoles, and Purines

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2-(Substituted amidino)acetamides and their 2-phenylazo-derivatives were cyclised with one-carbon-atom reagents to the corresponding pyrimidin-4(3*H*)-ones, identified by unambiguous synthesis from 4,6-dichloropyrimidine and by conversion into the corresponding 9-substituted hypoxanthines. The cyclisation of 2-(substituted amidino)-2-formamidoacetamide formate and hydrochloride salts to the isomeric ring and exocyclic *N*-substituted aminoimidazolecarboxamides was studied. The imidazolecarboxamides were converted, where possible, into the 3- or 9-substituted hypoxanthines.

2-AMIDINOACETAMIDE (1a) and its 2-amino-derivative (1h) constitute large parts of the skeletal backbones of pyrimidines, imidazoles, and purines, and the use of these derivatives in the syntheses of these compounds has been frequently reported.[1-6] 2-(Substituted amidino)acetamides [*e.g.* (1b—d)] and their 2-amino-derivatives [*e.g.* (1i—k)] should likewise be capable of use in the synthesis of appropriately substituted heterocyclic derivatives, but only a preliminary synthetic study has been reported.[7] This paper is concerned with the preparation

[1] D. J. Brown, 'The Pyrimidines' in 'The Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, Wiley–Interscience, New York, 1962.
[2] D. J. Brown, 'The Pyrimidines, Supplement 1' in 'The Chemistry of Heterocyclic Compounds,' ed. A. Weissberger and E. C. Taylor, Wiley–Interscience, New York, 1970.
[3] E. Richter and E. C. Taylor, *J. Amer. Chem. Soc.*, 1956, **78**, 5848.
[4] E. Richter, J. E. Loeffler, and E. C. Taylor, *J. Amer. Chem. Soc.*, 1960, **82**, 3144.
[5] O. Vogl and E. C. Taylor, *J. Amer. Chem. Soc.*, 1959, **81**, 2472.
[6] E. Shaw and D. W. Woolley, *J. Biol. Chem.*, 1949, **181**, 89
[7] E. Shaw, *J. Org. Chem.*, 1965, **30**, 3371.

of such substituted amidinoacetamides and with a general study of their potential as synthetic precursors of heterocycles. Benzyl, cyclohexyl, and 2-hydroxyethyl groups were used as substituents.

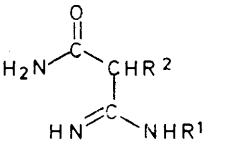
The 2-alkylamidinoacetamide (1b—d) hydrochlorides were prepared by treatment of an ethanolic solution of the appropriate amine with ethyl cyanoacetimidate hydrochloride.[7] Coupling of the amidine hydrochlorides with benzenediazonium chloride followed by neutralisation with aqueous alkali produced the 2-phenylazo-derivatives (1e—g). Cyclisation of the alkylamidinoacetamides (1b—d) and the phenylazo-derivatives (1e—g) with formamide and ethanolic sodium ethoxide gave respectively the 6-alkylaminopyrimidin-4(3*H*)-ones (2b—d) and their 5-phenylazo-derivatives (2e—g). The cyclisation processes were followed by t.l.c. [solvent (A)] and in no case was there evidence of formation of a ring-*N*-substituted pyrimidinone of type (3).

The structures of the pyrimidinones (2b—g) were confirmed by unambiguous syntheses from 4,6-dichloropyrimidine.[8] Successive monoalkylaminolysis [2] of this compound with the three amines gave the 4-alkylamino-6-chloropyrimidines (4a—c), which were hydrolysed to the alkylaminopyrimidinones (2b—d) *via* the methoxy-derivatives (4d—f). Coupling of compounds (2b—d) with benzenediazonium chloride yielded the 5-phenylazopyrimidinones (2e—g).

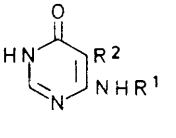
The structures of the phenylazopyrimidinones were further confirmed by their conversion into 9-alkylhypoxanthines (8a—c). Reduction of the 6-alkylamino-5-phenylazopyrimidin-4(3*H*)-ones to the 5-amino-analogues (2i—k) can be accomplished by a variety of chemical, electrolytic, and catalytic methods, but the method of choice in this work was catalytic hydrogenolysis over palladised charcoal. Closure of the imidazole ring to give the corresponding 9-alkylhypoxanthines (8a—c) can also be accomplished by a number of established procedures,[9-11] but formamide at 180 °C was the reagent of choice.

Direct conversion of 6-benzylamino-5-phenylazopyrimidin-4(3*H*)-one (2e) into 9-benzylhypoxanthine (8a) was accomplished by reductive formylation at room temperature and pressure with palladised charcoal in formic acid. Without isolation of the intermediate formamido-derivative, the formic acid solution was refluxed to yield the hypoxanthine. The yield of 9-benzylhypoxanthine was 55% (*cf.* 56% by the two-stage reduction and cyclisation process).

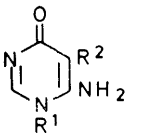
A ' one-stage ' nitrosation, reduction, and cyclisation of 6-benzylaminopyrimidin-4(3*H*)-one (2b) was investigated. A successful ' one-stage ' process has been achieved in the conversion of the unsubstituted 6-aminopyrimidin-4(3*H*)-one into hypoxanthine,[12] where the conditions used involved initial nitrosation with sodium nitrite in formic acid–formamide below 10 °C followed by reduction of the nitroso-derivative with sodium dithionite and subsequent cyclisation at 180 °C. These conditions with the aminopyrimidinone (2b) gave mainly unchanged starting material. By replacing the formic acid with hydrochloric acid and allowing the nitrosation to proceed at room temperature, a 26% yield of pure 9-benzylhypoxanthine was obtained.



(1)



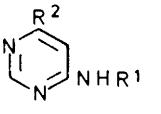
(2)



(3)

| | $R^1$ | $R^2$ |
|---|---|---|
| a; | H | H |
| b; | $PhCH_2$ | H |
| c; | $C_6H_{11}$ | H |
| d; | $HO[CH_2]_2$ | H |
| e; | $PhCH_2$ | $PhN_2$ |
| f; | $C_6H_{11}$ | $PhN_2$ |
| g; | $HO[CH_2]_2$ | $PhN_2$ |

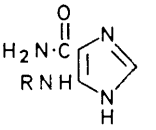
| | $R^1$ | $R^2$ |
|---|---|---|
| h; | H | $NH_2$ |
| i; | $PhCH_2$ | $NH_2$ |
| j; | $C_6H_{11}$ | $NH_2$ |
| k; | $HO[CH_2]_2$ | $NH_2$ |
| l; | $PhCH_2$ | NH·CHO |
| m; | $C_6H_{11}$ | NH·CHO |
| n; | $HO[CH_2]_2$ | NH·CHO |



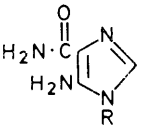
(4)

| | $R^1$ | $R^2$ |
|---|---|---|
| a; | $PhCH_2$ | Cl |
| b; | $C_6H_{11}$ | Cl |
| c; | $HO[CH_2]_2$ | Cl |

| | $R^1$ | $R^2$ |
|---|---|---|
| d; | $PhCH_2$ | OMe |
| e; | $C_6H_{11}$ | OMe |
| f; | $HO[CH_2]_2$ | OMe |



(5)



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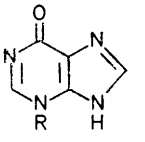
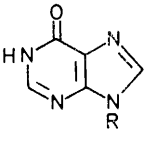


(7)



(8)

| | R |
|---|---|
| a; | $PhCH_2$ |
| b; | $C_6H_{11}$ |
| c; | $HO[CH_2]_2$ |

An alternative route to hypoxanthines involves a preformed imidazole nucleus. The preparation of the key intermediate 2-benzylamidino-2-formamidoacetamide (11) formate salt in 80% yield by reductive formylation of

[8] R. Hull, *J. Chem. Soc.*, 1951, 2214.
[9] J. H. Lister, *Rev. Pure and Appl. Chem.* (*Australia*), 1961, **11**, 178.
[10] R. K. Robins, ' The Purines and Related Ring Systems ' in ' Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1967, vol. 8, ch. 3.
[11] J. A. Montgomery and C. Temple, *J. Amer. Chem. Soc.*, 1958, **80**, 409.
[12] Kyowa Fermentation Industry Co. Ltd., Fr. P. 1,415,149 (*Chem. Abs.*, 1966, **64**, 5116).

2-benzylamidino-2-phenylazoacetamide (1e) with zinc and formic acid has been reported.[7] In the present work, catalytic reductive formylation with palladised charcoal in formic acid at room temperature and pressure proved more convenient as well as providing a higher yield (90%).

Shaw [7] cyclised the 2-benzylamidino-2-formamidoacetamide (1l) formate by refluxing in acetonitrile to yield as the main product (60%) the exocyclic *N*-substituted isomer (5a), only a trace of the ring-*N*-substituted isomer (6a) being formed. Refluxing in methanolic sodium methoxide, however, gave the ring-*N*-substituted isomer (6a) as the main product (39%), with only about 6% of the exocyclic substituted isomer (5a). The structures of these imidazoles were confirmed b conversion into the 3- and 9-benzylhypoxanthines [(7a) and (8a), respectively].

In the present work, the scope of this synthetic method was investigated by using *N*-cyclohexyl and *N*-2-hydroxyethyl analogues. 2-Cyclohexylamidino-2-formamidoacetamide (1m) formate salt was prepared in crystalline form without difficulty, but the formate salt of the 2-hydroxyethyl derivative (1n) could only be obtained as a gum, which gradually decomposed. 2-Cyclohexylamidino-2-formamidoacetamide (1m) formate is sparingly soluble in boiling acetonitrile and sufficient absolute ethanol to complete dissolution was therefore added. The cyclisation was followed by t.l.c. [solvent (B)] and equilibration of starting material with products was complete in 1½—2 h. Only a negligible amount of the ring-*N*-substituted imidazole (6b) was obtained, and the exocyclic *N*-substituted isomer (5b) was formed as a pale yellow water-insoluble gum. The imidazole was finally isolated as the crystalline toluene-*p*-sulphonate, but the yield of 50% (*cf.* 60% for the benzylimidazole) possibly reflects the use of a hydroxylic solvent in the cyclisation procedure. The structure of the salt was confirmed by its conversion into 3-cyclohexylhypoxanthine (7b) by refluxing a solution of the sulphonate in triethyl orthoformate for 30 min.

Attempts to cyclise the 2-cyclohexylamidino-2-formamidoacetamide (1m) formate salt in refluxing methanolic sodium methoxide resulted in tarry products, from which no pure compounds were isolated.

The limitations of synthesising 3- and 9-substituted hypoxanthines *via* a preformed imidazole nucleus stimulated efforts to achieve direct conversion of the 2-alkylamidino-2-formamidoacetamide formate salts into the hypoxanthines. Triethyl orthoformate proved the most successful formylating and cyclising reagent. Formamide, diethoxymethyl acetate, and triethyl orthoformate–acetic anhydride all proved highly destructive. The benzyl and cyclohexyl formate salts, after 2 h under gentle reflux in triethyl orthoformate, provided the 3-substituted hypoxanthines (7a and b) in 67 and 82% yields, respectively. Attempted conversion of the 2-hydroxyethyl formate gum directly into the hypoxanthine resulted in excessive decomposition.

Attention was next directed to the possibility of using the hydrochlorides of the 2-alkylamidino-2-formamidoacetamides (1l—n) in the direct synthesis of hypoxanthines. The hydrochlorides were prepared from the corresponding formates by treatment with an excess of methanolic hydrogen chloride. The hydrochlorides were refluxed for 5 min in triethyl orthoformate–dimethylformamide. T.l.c. [solvent (B)] showed the formation of both hypoxanthine isomers in each case but, in a number of runs, the benzyl and cyclohexyl hydrochlorides gave respectively, chromatographically pure 3-benzyl- and 3-cyclohexyl-hypoxanthines (7a and b) in 60—65% yield. Surprisingly, the 2-hydroxyethyl hydrochloride yielded the 9-substituted hypoxanthine (8c) as the predominant isomer, in 60% yield.

## EXPERIMENTAL

M.p.s. were determined on an electrothermal melting point apparatus. U.v. spectra were determined with a Unicam SP 1800A spectrophotometer. I.r. spectra were recorded on a Perkin-Elmer 157G spectrophotometer. Thin-layer chromatograms were run on Eastman Chromagram sheets and paper chromatograms on Whatman No. 1 paper by the ascending technique; solvent systems were (A) 50% formic acid–water–ethyl acetate (1 : 3 : 6), (B) butan-1-ol–glacial acetic acid–water (7 : 3). Spots were located by illumination with filtered u.v. light or by treatment with iodine vapour.

U.v. spectra of pyrimidines and hypoxanthines *

| Compound | $\lambda_{max.}$/nm (0.1N-NaOH) | log ε | $\lambda_{max.}$/nm (0.1N-HCl) | log ε |
|---|---|---|---|---|
| (2b) | 258 | 3.68 | 262 | 4.02 |
| (2c) | 256 | 3.78 | 262 | 4.08 |
| (2d) | 256 | 3.66 | 261 | 4.09 |
| (2e) | 244 | 4.32 | | |
| | 386 | 4.24 | | |
| (2f) | 244 | 4.34 | | |
| | 386 | 4.32 | | |
| (2g) | 243 | 4.28 | | |
| | 384—386 | 4.27 | | |
| (2i) | *236* | *3.65* | 262 | 4.05 |
| (2j) | *234* | *3.54* | 262 | 3.97 |
| (2k) | *234* | *3.56* | 262 | 3.85 |
| (4a) | 246 | 3.97 | 258 | 4.06 |
| | *278* | *3.31* | 261 | 4.06 |
| (4b) | 248 | 4.08 | 254 | 4.08 |
| | 278—280 | 3.41 | *260* | *4.06* |
| (4c) | 245 | 4.14 | *254—256* | *4.24* |
| | 274—278 | 3.55 | 258 | 4.26 |
| (4d) | 244 | 4.02 | 258 | 4.10 |
| (4e) | 247 | 3.98 | 255 | 4.10 |
| (4f) | 246 | 4.01 | 256 | 4.10 |
| (7b) | 265 | 4.06 | 254 | 4.03 |
| | *274* | *4.03* | | |
| (8c) | 256 | 4.06 | 250 | 4.05 |
| | *260* | *4.01* | | |

* Inflections in italics.

2-*Alkylamidinoacetamide* (1b—d) *Hydrochlorides*.—These were prepared by treatment of ethyl cyanoacetimidate hydrochloride with the appropriate amine.[7] 2-Benzylamidinoacetamide (1b) hydrochloride (60%) had m.p. 159—160° (from ethanol) (lit.,[7] 158—160°). 2-*Cyclohexylamidinoacetamide* (1c) *hydrochloride* (66.7%) had m.p. 220—222° (from ethanol) (Found: C, 49.15; H, 8.6; N, 19.15. $C_9H_{17}N_3O$,HCl requires C, 49.2; H, 8.25; N, 19.1%). 2-(2-*Hydroxyethylamidino*)*acetamide* (1d) *hydrochloride* (65.3%) had m.p. 148—149° (from ethanol) (Found:

C, 33.1; H, 6.4; N, 23.3. $C_5H_{11}N_3O_2$,HCl requires C, 33.05; H, 6.6; N, 23.15%).

2-*Alkylamidino*-2-*phenylazoacetamides* (1e—g). A solution of benzenediazonium chloride, prepared by careful addition of aqueous sodium nitrite (7.6 g in 80 ml) to aniline (9.3 g) in 6N-hydrochloric acid (50 ml) so that the temperature was maintained at 5—10 °C, was added at room temperature to a vigorously stirred [3] solution of the appropriate alkylamidinoacetamide (1b—d) hydrochloride (0.1 mol) in water (100 ml). Concentrated aqueous sodium acetate was then added until the pH was 4—5 and the amidinophenylazoacetamide was precipitated either as an oil or as yellow crystals. The pH was maintained at 4—5 for 2—3 h by frequent addition of sodium acetate solution.[13] The hydrochloride was then converted into the free base by addition of an excess of sodium acetate solution, the mixture usually going through a pasty phase. It was found advisable to adjust the pH to 8—9 with cold 4N-sodium hydroxide to ensure complete conversion into the base. Refrigeration overnight yielded yellow crystals, which were collected and washed with water. 2-Benzylamidino-2-phenylazoacetamide (1e) (84.6%) had m.p. 143—144° (from aqueous ethanol) (lit.,[7] 136—138°) (Found: C, 65.0; H, 5.8; N, 23.4. Calc. for $C_{16}H_{17}N_5O$: C, 65.0; H, 5.8; N, 23.7%). 2-*Cyclohexylamidino*-2-*phenylazoacetamide* (1f) (80.8%) had m.p. 155—156° (from aqueous ethanol) (Found: C, 62.4; H, 7.45; N, 24.2. $C_{15}H_{21}N_5O$ requires C, 62.75; H, 7.4; N, 24.4%). 2-(2-*Hydroxyethylamidino*)-2-*phenylazoacetamide* (1g) (76.3%) had m.p. 132—133° (from chloroform) (Found: C, 52.55; H, 6.4; N, 27.8. $C_{11}H_{15}N_5O_2$ requires C, 53.0; H, 6.05; N, 27.5%).

6-*Alkylaminopyrimidin*-4(3H)-*ones* (2b—d).—(*a*) A mixture of the alkylamidinoacetamide (1b—d) hydrochloride (0.01 mol), formamide (0.68 g), and sodium ethoxide [from sodium (0.69 g)] was refluxed in ethanol (70 ml) for 2 h. The solvent was removed *in vacuo* and the residue dissolved in water (20 ml). Addition of 2N-hydrochloric acid with stirring until the pH was 4—5 yielded white crystals, which were collected and washed with cold water. 6-Benzylaminopyrimidin-4(3*H*)-one (2b) (89.1%) had m.p. 241—242° (from ethanol) (lit.,[14] 230—234°) (Found: C, 65.55; H, 5.75; N, 20.4. Calc for $C_{11}H_{11}N_3O$: C, 65.35; H, 6.0; N, 20.8%). 6-*Cyclohexylaminopyrimidin*-4(3H)-*one* (2c) (87.0%) had m.p. 266—269° (decomp.) (from ethanol) (charcoal) (Found: C, 62.45; H, 8.0; N, 21.7. $C_{10}H_{15}N_3O$ requires C, 62.15; H, 7.8; N, 21.75%).

The aqueous alkaline solution from the reaction of the 2-hydroxyethyl hydrochloride (1d) was passed down a column of ZeoCarb 225 ion-exchange resin ($H^+$ form; 50—100 mesh). The column was washed through with water until the eluate was transparent in the u.v. Evaporation gave white crystals of 6-(2-*hydroxyethylamino*)-*pyrimidin*-4(3H)-*one* (2d) (77.4%), m.p. 233—234° (from ethanol) (charcoal) (Found: C, 46.7; H, 6.15; N, 27.0. $C_6H_9N_3O_2$ requires C, 46.45; H, 5.85; N, 27.1%).

(*b*) A mixture of the 4-alkylamino-6-methoxypyrimidine (4d—f) (0.003 mol) and 11N-hydrochloric acid (16 ml) was refluxed for 2 h. The solution was evaporated *in vacuo* and the residue dissolved in the minimum of hot water. The cooled solutions from (4d) and (4e) were neutralised with aqueous 2N-ammonia, to give the pyrimidinones (2b) (35.1%) and (2c) (37.0%), respectively, both identical (mixed m.p. and i.r. spectra) with material obtained by method (*a*). The cooled solution from the 2-hydroxyethylaminopyrimidine (4f) was passed down a column of Amberlite ion-exchange resin CG45 ($OH^-$ form) (6 g) and the column was washed with water until the eluate was transparent in the u.v. Evaporation gave the 2-hydroxyethylaminopyrimidinone (2d) (55.5%), identical (mixed m.p. and i.r. spectra) with material obtained by method (*a*).

6-*Alkylamino*-5-*phenylazopyrimidin*-4(3H)-*ones* (2e—g).—(*a*) A mixture of the 2-alkylamidino-2-phenylazoacetamide (1e—g) (0.015 mol), formamide (2.04 g), and sodium ethoxide [from sodium (0.69 g)] was refluxed in ethanol (75 ml) for 2 h. The solvent was removed *in vacuo* and the orange pasty residue suspended in cold water (150 ml). 2N-Hydrochloric acid was added to the stirred suspension until the pH was 4—5, and after refrigeration overnight the orange crystals were filtered off and washed thoroughly with water. 6-*Benzylamino*-5-*phenylazopyrimidin*-4(3H)-*one* (2e) (69.9%) had m.p. 204—205° (from ethanol) (Found: C, 66.6; H, 5.05; N, 22.75. $C_{17}H_{15}N_5O$ requires C, 66.9; H, 4.95; N, 22.95%). 6-*Cyclohexylamino*-5-*phenylazopyrimidin*-4(3H)-*one* (2f) (76.5%) had m.p. 225—226° (from ethanol) (Found: C, 64.4; H, 6.4; N, 23.7. $C_{16}H_{19}N_5O$ requires C, 64.6; H, 6.45; N, 23.7%). 6-(2-*Hydroxyethylamino*)-5-*phenylazopyrimidin*-4(3H)-*one* (2g) (87.4%) had m.p. 248—249° (from ethanol) (Found: C, 55.45; H, 4.95; N, 27.0. $C_{12}H_{13}N_5O_2$ requires C, 55.6; H, 5.05; N, 27.15%).

(*b*) A stirred suspension of the 6-alkylaminopyrimidin-4(3*H*)-one (2b—d) (0.001 2 mol) was treated with 2N-sodium hydroxide until the pH was 8. A benzenediazonium chloride solution, prepared by adding aqueous sodium nitrite (0.09 g in 2 ml) to a stirred mixture of aniline (0.12 g) and 6N-hydrochloric acid (1 ml) maintained at 5—10° C, was added to the stirred alkaline solution at room temperature. After 1 h, the pH of the mixture was adjusted to 4—5 with a few drops of 2N-hydrochloric acid and the orange crystals were collected and washed with water. The pyrimidinones (2b, c, and g) gave, respectively, the phenylazo-derivatives (2e) (64.9%), (2f) (65.0%), and (2g) (48.4%), identical (mixed m.p. and i.r. spectra) with materials obtained by method (*a*).

4-*Alkylamino*-6-*chloropyrimidines* (4a—c).—A mixture of 4,6-dichloropyrimidine (5.0 g) and the appropriate amine (redistilled; 0.1 mol) in ethanol (50 ml) was heated in a sealed glass tube at 100 °C for 1 h. The cooled mixture was evaporated *in vacuo* and the oily residue thoroughly triturated with water. Decantation of the water followed by evaporation *in vacuo* yielded buff-coloured crystals. 4-Benzylamino-6-chloropyrimidine (4a) (69.1%) had m.p. 122—123° (from benzene and light petroleum) (lit.,[15] 121°). 4-*Chloro*-6-*cyclohexylaminopyrimidine* (4b) (74.5%) had m.p. 120—121: (from benzene and light petroleum) (Found: C, 56.55; H, 7.1; N, 19.75. $C_{10}H_{14}ClN_3$ requires C, 56.75; H, 6.7; N, 19.85%). 4-*Chloro*-6-(2-*hydroxyethylamino*)*pyrimidine* (4c) (69.8%), had m.p. 115—116° (from benzene and methanol) (Found: C, 41.45; H, 4.9; N, 24.3. $C_6H_8ClN_3O$ requires C, 41.5; H, 4.65; N, 24.2%).

4-*Alkylamino*-6-*methoxypyrimidines* (4d—f).—A solution of the 4-alkylamino-6-chloropyrimidine (4a—c) (0.006 4 mol) and sodium methoxide [from sodium (0.45 g)] in methanol (9 ml) was heated under reflux for 1.5 h with exclusion of

[13] L. H. Smith, jun., and P. Yates, *J. Amer. Chem. Soc.*, 1954, **76**, 6080.

[14] C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, 1960, **82**, 3971.

[15] C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, 1958, **80**, 2185.

moisture. After cooling, the solvent was removed *in vacuo*. [In the case of (4c), a stream of $CO_2$ was bubbled through during cooling.] The white residue was crystallised from water and then sublimed under vacuum. 4-*Benzylamino*-6-*methoxypyrimidine* (4d) (59.1%) (subl. 160—170° at $10^{-4}$ mmHg) had m.p. 137—138° (Found: C, 66.95; H, 6.3; N, 19.15. $C_{12}H_{13}N_3O$ requires C, 66.95; H, 6.1; N, 19.55%). 4-*Cyclohexylamino*-6-*methoxypyrimidine* (4e) (82.7%) (subl. 100—110° at $10^{-4}$ mmHg) had m.p. 96—97° (Found: C, 63.6; H, 8.25; N, 20.25. $C_{11}H_{17}N_3O$ requires C, 63.75; H, 8.25; N, 20.3%). 4-(2-*Hydroxyethylamino*)-6-*methoxypyrimidine* (4f) (64.7%) (subl. 90—100° at $10^{-4}$—$10^{-5}$ mmHg) had m.p. 94.5—95.0° (Found: C, 50.25; H, 6.9; N, 24.7. $C_7H_{11}N_3O_2$ requires C, 49.7; H, 6.55; N, 24.85%).

6-*Alkylamino*-5-*aminopyrimidin*-4(3H)-*ones* (2i—k).—A mixture of palladised charcoal (10%; 0.8 g) and the 6-alkylamino-5-phenylazopyrimidin-4(3*H*)-one (2e—g) (0.003 mol) in ethanol (75 ml) was hydrogenated at room temperature and pressure with vigorous agitation, until the theoretical quantity of hydrogen had been absorbed. After removal of the catalyst, the solution was evaporated *in vacuo* to a gummy residue, which was triturated thoroughly with ether to provide pale pink crystals. 5-*Amino*-6-*benzylaminopyrimidin*-4(3H)-*one* (2i) (69.4%) had m.p. 184.5—185.5° (from ethanol) (Found: C, 61.0; H, 5.6; N, 25.85. $C_{11}H_{12}N_4O$ requires C, 61.1; H, 5.6; N, 25.9%). 5-*Amino*-6-*cyclohexylaminopyrimidin*-4(3H)-*one* (2j) (80.0%) had m.p. 210—212° (from ethanol) (Found: C, 58.0; H, 8.0; N, 26.9. $C_{10}H_{16}N_4O$ requires C, 57.7; H, 7.75; N, 26.9%). 5-*Amino*-6-(2-*hydroxyethylamino*)*pyrimidin*-4(3H)-*one* (2k) (78.4%) had m.p. 219—221° (from aqueous ethanol) (Found: C, 41.95; H, 6.05; N, 32.45. $C_6H_{10}N_4O_2$ requires C, 42.35; H, 5.9; N, 32.95%).

9-*Alkylhypoxanthines* (8a—c).— The 6-alkylamino-5-aminopyrimidin-4(3*H*)-one (2i—k) (0.001 mol) was heated in formamide (10 ml) for 1.5 h at 180 °C (oil-bath). Refrigeration caused deposition of white crystals. 9-Benzylhypoxanthine (8a) (82.2%) had m.p. 294—296° (from ethanol) (lit.,[16] >240°; lit.,[7] 295—297°). 9-Cyclohexylhypoxanthine (8b) (85.0%), had m.p. 264—268° (from ethanol) (lit.,[11] 273—275°). 9-(2-*Hydroxyethyl*)*hypoxanthine* (8c) (80.0%) had m.p. 287—290° (from ethanol) (Found: C, 46.95; H, 4.8; N, 31.4. $C_7H_8N_4O_2$ requires C, 46.65; H, 4.5; N, 31.1%).

*Conversion of* 6-*Benzylamino*-5-*phenylazopyrimidin*-4-(3H)-*one* (2e) *into* 9-*Benzylhypoxanthine* (8a).—Palladised charcoal (10%; 0.5 g), which had been moistened with water in order to minimise the tendency to explode with formic acid,[17] was added to a solution of the pyrimidinone (1.84 g) in formic acid (98%; 20 ml). The mixture was hydrogenated with vigorous agitation at room temperature and pressure until there was no further uptake of hydrogen (*ca.* 1 h). After removal of the catalyst by filtration, the formic acid solution was refluxed until the u.v. spectrum showed that conversion into the hypoxanthine was complete (*ca.* 4 h). The solution was evaporated *in vacuo* and the excess of formic acid removed by repeated concentration *in vacuo* with added water. The resultant syrup was triturated thoroughly with ether and the ether decanted. The residue was suspended in water (10 ml) and the solution adjusted to pH 8 by dropwise addition of concentrated ammonia. Refrigeration of the mixture followed by filtration yielded the hypoxanthine (0.75 g, 55%), identical (mixed m.p. and u.v. and i.r. spectra) with an authentic specimen.

*Conversion of* 6-*Benzylaminopyrimidin*-4(3H)-*one* (2b) *into* 9-*Benzylhypoxanthine* (8a).—The pyrimidinone (2b) was added to a stirred suspension of sodium nitrite (0.06 g) in formamide (1 ml). 6N-Hydrochloric acid (1 ml) was added dropwise at room temperature and no attempt was made to dissipate the heat evolved. A blue-green colour developed which changed finally to a reddish amber. The temperature of the solution was then raised to 120 °C (oil-bath) and sodium dithionite added until the solution was pale yellow. The temperature was further raised to 180 °C (oil-bath) and this temperature was maintained for 1 h. Some black residue was filtered from the hot mixture and the filtrate was cooled and refrigerated. Greenish coloured crystals which separated were collected and washed with a little cold ethanol. Recrystallisation from ethanol (charcoal) gave the hypoxanthine (0.04 g, 26.2%), identical (mixed m.p. and u.v. and i.r. spectra) with an authentic specimen.

2-*Alkylamidino*-2-*formamidoacetamide* (1l—n) *Formate Salts*.—The appropriate 2-alkylamidino-2-phenylazoacetamide (1e—g) (0.02 mol) was suspended in a mixture of formic acid (98%; 50 ml) and previously moistened palladised charcoal (10%; 2 g). The mixture was hydrogenated with vigorous shaking until there was no further uptake. The catalyst was filtered off and washed with formic acid and the filtrate concentrated *in vacuo* below 40 °C. The excess of formic acid was removed by repeated concentration *in vacuo* with added water and finally ethanol. The residue was triturated thoroughly with ether (*ca.* 150 ml) and the product filtered off. 2-Benzylamidino-2-formamidoacetamide (1l) formate salt (90%), white crystals, had m.p. 130—131° (from aqueous ethanol and ether) (lit.,[7] 131—132°). 2-*Cyclohexylamidino*-2-*formamidoacetamide* (1m) *formate salt* (85.0%), white crystals, had m.p. 143—145° (from aqueous ethanol and ether) (Found: C, 48.4; H, 7.4; N, 20.4. $C_{10}H_{18}N_4O_2,HCO_2H$ requires C, 48.5; H, 7.4; N, 20.55%). 2-Formamido-2-(2-hydroxyethylamidino)acetamide (1n) formate salt was a non-crystallisable gum, identified by conversion into the corresponding hydrochloride (see below).

2-*Alkylamidino*-2-*formamidoacetamide* (1l—n) *Hydrochlorides*.—The 2-alkylamidino-2-formamidoacetamide (1l—n) formate salt (2 g) was dissolved in the minimum of methanol, and methanolic hydrogen chloride was added dropwise until the solution was strongly acid to moist litmus paper. Ether was added gradually until, with scraping, precipitation started. After refrigeration, the white crystals were filtered off. 2-*Benzylamidino*-2-*formamidoacetamide* (1l) *hydrochloride hemihydrate* (90.0%) had m.p. 165—167° (decomp.) (from aqueous ethanol and ether) (Found: C, 47.45; H, 5.55; N, 20.1. $C_{11}H_{14}N_4O_2,HCl,0.5H_2O$ requires C, 47.25; H, 5.75; N, 20.05%). 2-*Cyclohexylamidino*-2-*formamidoacetamide* (1m) *hydrochloride* (79.0%) had m.p. 195—197° (decomp.) (from aqueous ethanol and ether) (Found: C, 45.65; H, 7.15; N, 20.7. $C_{10}H_{18}N_4O_2,HCl$ requires C, 45.7; H, 7.2; N, 21.3%). 2-*Formamido*-2-(2-*hydroxyethylamidino*)*acetamide* (1n) *hydrochloride* (74.0%) had m.p. 144—145° (decomp.) (from aqueous ethanol and ether) (Found: C, 32.45; H, 5.6; N, 24.4. $C_6H_{12}N_4O_3,HCl$ requires C, 32.1; H, 5.85; N, 24.95%).

[16] J. A. Montgomery and C. Temple, *J. Amer. Chem. Soc.*, 1961, **83**, 630.

[17] J. A. Montgomery, K. Hewson, R. F. Struck, and Y. F. Shealy, *J. Org. Chem.*, 1959, **24**, 256.

4(5)-*Cyclohexylaminoimidazole*-5(4)-*carboxamide* (5b) *Toluene*-p-*sulphonate Salt.*—2-Cyclohexylamidino-2-formamidoacetamide (1m) formate salt (1.0 g) was refluxed in acetonitrile (20 ml), sufficient ethanol being added at the boil to complete dissolution. After 2 h, the solution was evaporated to dryness *in vacuo* and the residue dissolved in water (10 ml). Cold N-sodium hydroxide was added until the solution was alkaline to litmus. A small amount of alkali-insoluble matter was filtered off and the pH of the filtrate adjusted to 5 by dropwise addition of glacial acetic acid. A pale yellow gum was deposited and the aqueous layer was removed by decantation. The gum was dissolved in chloroform and the solution dried ($Na_2SO_4$) and treated with a chloroform slurry of toluene-*p*-sulphonic acid monohydrate (0.5 g). The resulting precipitate was filtered off and washed thoroughly with ether to give white crystals of the *toluene*-p-*sulphonate* (50.0%), m.p. 242—244° (decomp.) (from ethanol) (Found: C, 53.85; H, 6.3; N, 14.7. $C_{17}H_{24}N_4O_4S$ requires C, 53.65; H, 6.35; N, 14.75%).

3-*Alkylhypoxanthines* (7a *and* b).—(*a*) A suspension of 4(5)-cyclohexylaminoimidazole-5(4)-carboxamide (5b) toluene-*p*-sulphonate salt (0.5 g) in triethyl orthoformate (20 ml) was refluxed for 0.5 h. The resulting mixture was evaporated *in vacuo*, the residue dissolved in water (5 ml), and sodium hydrogen carbonate solution added carefully to neutrality. Refrigeration and filtration gave white crystals of 3-*cyclohexylhypoxanthine* (7b) (88.0%), m.p. 304—306° (from ethanol) (Found: C, 60.65; H, 6.8; N, 25.35. $C_{11}H_{14}N_4O$ requires C, 60.5; H, 6.45; N, 25.65%).

(*b*) The 2-alkylamidino-2-formamidoacetamide (1l or m) formate salt in triethyl orthoformate (50 ml) was heated under reflux for 2 h. The dark coloured solution gradually deposited a grey solid. Refrigeration followed by filtration gave the product. 3-Benzylhypoxanthine (7a) (67.0%), m.p. 281—282° (from ethanol) (charcoal), was identical (mixed m.p. and i.r. and u.v. spectra) with a specimen obtained by an unambiguous route.[7] 3-Cyclohexylhypoxanthine (7b) (82.0%) (from ethanol) (charcoal) was identical (mixed m.p. and i.r. and u.v. spectra) with an authentic specimen. T.l.c. [solvent (B)] of the filtrate, in both cases, showed traces of the 9-substituted hypoxanthine.

*Cyclisation of* 2-*Alkylamidino*-2-*formamidoacetamide* (1l—n) *Hydrochlorides to Hypoxanthines.*—The hydrochloride (0.5 g) in triethyl orthoformate (2 ml) and dimethylformamide (4 ml) was refluxed for 5 min. The pale yellow solution was concentrated *in vacuo* and the oily residue triturated with ethanol. Refrigeration followed by filtration gave the product. The 3-benzylhypoxanthine (7a) (64.0%), 3-cyclohexylhypoxanthine (7b) (60.0%), and 9-(2-hydroxyethyl)hypoxanthine (8c) (60.0%) were all identical (mixed m.p. and i.r. and u.v. spectra) with authentic specimens. T.l.c. [solvent (B)] of the filtrate, in each case, showed the presence of the other isomeric hypoxanthine.

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