moved by consecutive preparative thin layer chromatography, treatment with activated carbon, and again preparative layer chromatography. The product so obtained was colorless but no change in the physical measurements cited above was noted.

**Registry No.**—**1a**, 53-43-0; **1b**, 29163-23-3; **2**, 31020-62-9; **3**, 31020-63-0; **4**, 31020-64-1; **5**, 31020-65-2; **6a**, 31020-66-3; **6b**, 31020-67-4; **7a**, 31020-68-5; **7b**, 31020-69-6; **8a**, 31020-70-9; **8b**, 31107-24-1; (20*R*)-**9a**, 31020-71-0; (20*S*)-**9a**, 31020-72-1; **9b**, 31107-25-2; **10**, 31020-73-2; **11**, 14414-50-7.

# A New, General Synthesis of 2-, 8-, and 9-Substituted Adenines[1]

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A new synthesis of adenine derivatives is described which involves the initial conversion of a 4,6-diamino-5-nitrosopyrimidine to a 7-aminofurazano[3,4-*d*]pyrimidine (**2**) by lead tetraacetate oxidation, introduction of the eventual adenine 9 and 8 substituents by reaction of **2** with an alkylamine followed by acylation (**3** → **4**), and reductive cleavage of the furazan ring to give an intermediate **5** which recyclizes to the desired adenine derivative **6**. All reactions proceed under mild conditions, and all substituents are introduced unambiguously.

The classical and still most widely employed synthetic route to adenine and adenine derivatives, compounds of ubiquitous natural occurrence and extreme biological importance, is that of Traube involving cyclization of a 4,5,6-triaminopyrimidine with reagents such as formamide and other carboxamides, triethyl orthoformate–acetic anhydride (or diethoxymethyl acetate), carboxylic acids, carbon disulfide, and sodium dithioformate.[3] This approach possesses several intrinsic disadvantages in that (a) reaction conditions required for ring closure are often severe and (b) in its application to 9-substituted adenines, an inevitable ambiguity arises as to the direction of ring closure.[4-6]

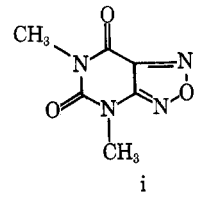
The most commonly employed alternate route involves aminolysis of a purine derivative carrying a 6-chloro, thio, methylthio, methylsulfinyl, methylsulfonyl, or sulfonate substituent, but here as well severe reaction conditions are often required and the requisite purine intermediates are tedious to prepare.[7] 9-Substituted adenines may also be prepared by alkylation, but, since both 7- and 9-alkylated derivatives are often obtained, this process is also inherently ambiguous.[8]

We describe in this paper a new approach to the synthesis of adenines which is widely applicable and which possesses two important special features: (a) all reactions proceed under mild conditions and (b) it introduces all substituents, including the critical 9 substituent, unambiguously.

This new route to adenines involves the following steps: (a) oxidation of a 4,6-diamino-5-nitrosopyrimidine (**1**) with lead tetraacetate to a 7-aminofurazano-[3,4-*d*]pyrimidine (**2**); (b) reaction of **2** with an alkylamine to give a 7-alkylaminofurazano[3,4-*d*]pyrimidine (**3**); (c) formylation, acylation, or aroylation of the exocyclic alkylamino group to give **4**; and (d) reductive cleavage of the furazan ring, which is followed by spontaneous recyclization to the desired adenine (**6**). In this manner, the eventual 9 substituent is determined by an appropriate choice of the alkylamine used in step b, and the eventual 8 substituent is determined by the choice of reagent employed in step c. The eventual 2 substituent is determined in the usual manner at the initial stage of pyrimidine synthesis. The furazan ring serves to protect both the potential 6-amino group and 7-nitrogen atom while allowing the unequivocal introduction of both the eventual 9-nitrogen and 8-carbon atoms, together with their desired substituents in the target adenine. In addition, it imparts to the system a remarkable reactivity (see discussion below) which allows step b to proceed under very mild conditions.

**Preparation of 7-Aminofurazano[3,4-*d*]pyrimidines (2). Step a.**—We have found that a wide variety of 2-substituted 4,6-diamino-5-nitrosopyrimidines (**1**) are converted smoothly and at room temperature to 7-aminofurazano[3,4-*d*]pyrimidines (**2**) upon treatment in acetic acid solution with 1 equiv of lead tetraacetate.[9] The requisite 5-nitrosopyrimidines are readily available *via* thermal cyclization of amidine salts of isonitrosomalononitrile[10] or by direct nitrosation of the corresponding 4,6-diaminopyrimidines.[11]

Proof of the structure of **2** rests upon nmr and mass spectral data, elemental analyses, and subsequent chem-



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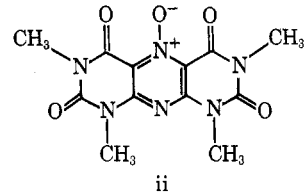


ii

(1) We acknowledge with gratitude financial support for this work from Eli Lilly and Co. and from the National Science Foundation and the Japan Society for the Promotion of Science, Office of International Programs, U. S.-Japan Committee on Scientific Cooperation, Grants No. GF-390 and 5R012.

(2) NSF Predoctoral Fellow, 1968–1971.

(3) For an excellent review of these methods, see R. K. Robins, in "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1967, pp 142–144.

(4) G. A. Howard, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 556 (1945), and preceding papers in this series.

(5) R. Hull, *ibid.*, 2746 (1958).

(6) H. C. Koppel, D. E. O'Brien, and R. K. Robins, *J. Amer. Chem. Soc.*, **81**, 3046 (1959).

(7) For numerous examples see ref 3, p 319.

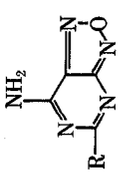
(8) J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 318 (1944); for additional examples see ref 3, p 372.

(9) Extrapolation of this oxidative procedure to 1,3-dimethyl-5-nitroso-6-aminouracil was found to give a modest (19%) yield of 4,6-dimethyl-5,7-(4*H*,6*H*)-furazano[3,4-*d*]pyrimidinedione (i); the major product, however, was 1,3,6,8-tetramethyl-2,4,5,7-(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone 5-*N*-oxide (ii). Details of this surprising reaction will be given in a separate paper.

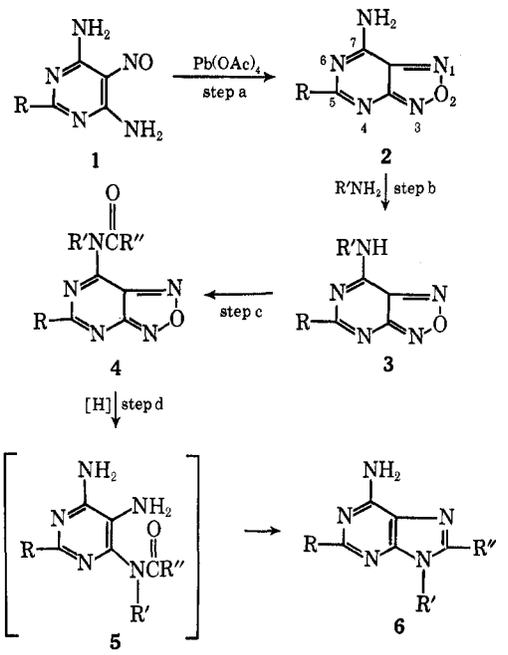
(10) E. C. Taylor, O. Vogl, and C. C. Cheng, *J. Amer. Chem. Soc.*, **81**, 2442 (1959).

(11) D. J. Brown, "The Pyrimidines," Interscience, New York, N. Y., 1962.

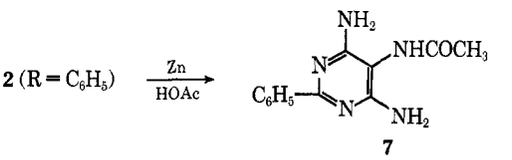
TABLE I
7-AMINOFURAZANO[3,4-*d*]PYRIMIDINES (2)



| R | Registry no. | Mp, °C | Recrystn solvent | Yield, % | Calcd (found), % C | H | N | S | Nmr shift (τ) for R | Uv, $\lambda_{max}^{CH_3OH}$, nm (log ε) |
|---|---|---|---|---|---|---|---|---|---|---|
| H | 22003-13-0 | 290 dec | Acetic acid | 82 | 35.04 (34.86) | 2.21 (2.21) | 51.08 (50.95) | | 1.60 | 210 (4.18), 253 (sh, 3.08), 340 (3.83) |
| $CH_3$ | 30708-66-8 | 239–241 dec | Ethanol | 86 | 39.73 (39.82) | 3.33 (3.23) | 46.34 (46.06) | | 7.63 | 210 (4.24), 337 (3.80) |
| $H_2N$ | 30745-07-4 | 340 dec | Aqueous DMF | 87 | 31.58 (31.31) | 2.65 (2.57) | 55.25 (54.80) | | 3.1 (broad) | 210 (4.12), 283 (3.77), 340 (3.55) |
| $(CH_3)_2N$ | 30708-67-9 | 259–261 | Aqueous DMF | 75 | 40.00 (40.12) | 4.48 (4.32) | 46.65 (46.49) | | 6.83 | 232 (4.08), 298 (3.84), 360 (3.52) |
| $CH_3S$ | 30708-68-0 | 248–249 | Aqueous DMF | 72 | 32.78 (32.52) | 2.75 (2.66) | 38.23 (38.04) | 17.50 (17.67) | 7.50 | 244 (3.86), 308 (4.06), 352 (3.60) |
| $C_6H_5$ | 30720-36-6 | 230–232 | Ethanol | 82 | 56.33 (56.22) | 3.31 (3.55) | 32.85 (32.64) | | 1.7–2.6 (multiplets) | 226 (4.04), 265 (4.13), 274 (4.11), 294 (4.06) 310 (sh, 3.96), 344 (3.79) |




ical conversions (*vide infra*). Furthermore, the structure of **2** (R = H) has been determined by a single-crystal X-ray analysis.[12] The structure of **2** (R = $C_6H_5$) was also confirmed by reduction to 2-phenyl-4,6-diamino-5-acetamidopyrimidine (**7**) by brief heating with acetic acid in the presence of zinc dust. This product was identical with an authentic sample prepared by acetylation of 2-phenyl-4,5-6-triaminopyrimidine.




7-Aminofurazano[3,4-*d*]pyrimidines prepared by the above procedure are listed in Table I.

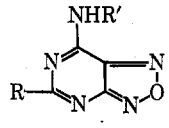
**Conversion to 7-Alkylaminofurazano[3,4-*d*]pyrimidines (3). Step b.**—A notable chemical property of these 7-aminofurazano[3,4-*d*]pyrimidines is the unusual facility with which they undergo nucleophilic attack at position 7. Thus, treatment with alkylamines *at room temperature or below* results in displacement of the 7-amino group with the formation of the corresponding 7-alkylamino derivative. Table II lists the 7-alkylamino derivatives prepared by this procedure.

The extraordinary ease with which nucleophilic displacement of the 7-amino group in **2** occurs contrasts sharply with the relatively vigorous conditions necessary for the analogous displacement of an amino group from the 4 position of the isoelectronic pteridines[13,14] and with the conditions required for displacement of the 7-amino group from the related thiadiazolo[3,4-*d*]pyrimidine system.[15] Molecular orbital calculations carried out on **2** (R = H)[16] indicate considerable charge separation in the ground state. In particular, an unus-

(12) We are indebted to Professor Eli Shefter, Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, for the X-ray analysis; details will be published independently.
(13) E. C. Taylor and C. K. Cain, *J. Amer. Chem. Soc.*, **73**, 4384 (1951).
(14) E. C. Taylor, *ibid.*, **74**, 1648 (1952).
(15) Y. F. Shealy and C. A. O'Dell, *J. Org. Chem.*, **27**, 2135 (1964).
(16) E. C. Taylor, Y. Maki, and B. E. Evans, *J. Amer. Chem. Soc.*, **91**, 5181 (1969).

TABLE II

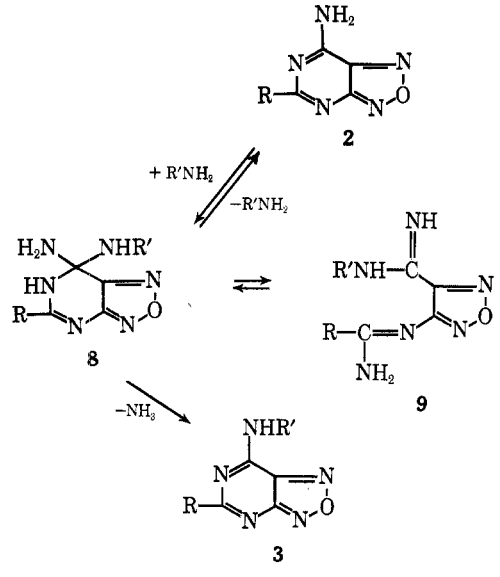
7-SUBSTITUTED AMINOFURAZANO[3,4-*d*]PYRIMIDINES (3)

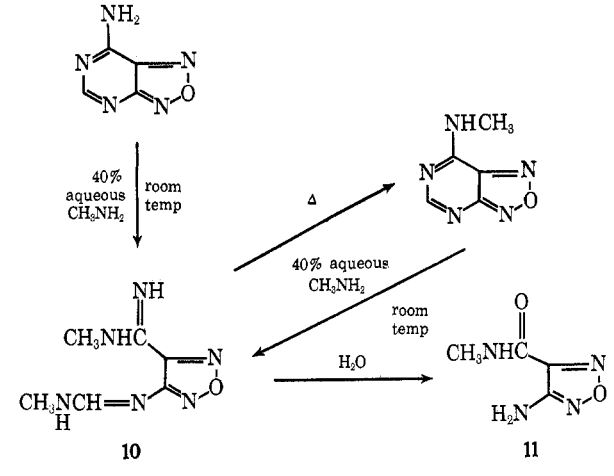


| R | R′ | Registry no. | Method | Mp, °C | Recrystn solvent | Yield, % | Calcd (found), % C | H | N | S | Nmr shift τ for R | R′ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | $CH_3$ | 30720-37-7 | A | 230-231 | Ethanol | 88 | 43.63 (43.89) | 4.27 (4.19) | 42.41 (42.65) | | 7.58 | 6.95 |
| $CH_3$ | $C_6H_{11}$ | 30720-38-8 | B | 95-96 | Aqueous ethanol | 88 | 56.63 (56.48) | 6.48 (6.34) | 30.03 (29.83) | | 7.52 | 8-9 (multiplet) |
| $H_2N$ | $CH_3$ | 30720-39-9 | C | 310 dec | Aqueous DMF | 86 | 36.14 (35.97) | 3.64 (3.50) | 50.59 (50.79) | | 2.9 (broad) | 7.07 |
| $(CH_3)_2N$ | $CH_3$ | 30720-40-2 | A | 183-184 | Aqueous DMF | 90 | 43.29 (43.43) | 5.19 (5.10) | 43.28 (43.26) | | 6.85 | 7.05 |
| $CH_3S$ | $CH_3$ | 30720-41-3 | A | 158-159 | Methanol | 95 | 36.54 (36.40) | 3.58 (3.57) | 35.51 (35.27) | 16.26 (16.26) | 7.47 | 6.95 |
| $CH_3S$ | $C_2H_5$ | 30720-42-4 | A | 137-138 | Methanol | 87 | 39.80 (39.90) | 4.29 (4.45) | 33.16 (33.12) | 15.18 (15.18) | 7.47 | 6.40, 8.72 |
| $C_6H_5$ | $CH_3$ | 30720-43-5 | C | 219-220 | Ethanol | 90 | 58.20 (58.76) | 4.00 (4.30) | 30.85 (31.14) | | 1.7-2.5 | 6.81 |

ually low charge density (0.511) at C-7 accounts readily for the observed reactivity of **2** toward nucleophiles.[17]

Mechanisms involving ring opening and subsequent reclosure have been proposed, and in some cases validated, for amino group displacement (exchange amination) in pyrimidines and fused pyrimidines.[13,14,18-23] An analogous ring-opening, ring-closure sequence for the conversion of **2** to **3** would include the equilibrium **8** ⇄ **9**. Amino group exchange could also proceed directly *via* the $sp^3$ intermediate **8**, however, and our experimental results appear to indicate that this is indeed the course which is followed. Thus, we have prepared independently (see Experimental Section) the ring-opened bisamidine **10** (analogous to **9**) and have found that it cyclizes to 7-methylaminofurazano[3,4-*d*]pyrimidine (**3**, R = H; R′ = $CH_3$) only on vigorous heating. Since the conversion of **2** to **3** occurs at room temperature, it therefore seems unlikely that the equilibrium **8** ⇄ **9** is important.




**Formation of 7-Acylaminofurazano[3,4-*d*]pyrimidines (4). Step c.**—Formylation, acylation, or aroylation of the 7-alkylaminofurazano[3,4-*d*]pyrimidine (**3**) introduces the eventual purine 8-carbon atom with its substituent. These reactions are essentially quantitative and proceed under mild conditions. The products thus obtained are listed in Table III.

**Synthesis of Adenines. Step d.**—Reduction of **4** either by low-pressure catalytic hydrogenation in acetic acid solution, or with zinc dust in acetic acid, results in smooth conversion to adenines **6** in high yield. This conversion apparently involves initial hydrogenolysis of the furazan ring to give an intermediate 4-acylamino-5,6-diaminopyrimidine (**5**) which then cyclizes. Confirmation of this reaction course was readily achieved by catalytic reduction of **4** [R = $N(CH_3)_2$; R′ = R″ = H] in ethanol solution, which yielded 2-dimethylamino-4,5-diamino-6-formylaminopyrimidine [**5**, R = $N(CH_3)_2$; R′ = R″ = H]. Dissolution of this latter compound in acetic acid resulted in spontaneous cyclization to 2-dimethylaminoadenine [**6**, R = $N(CH_3)_2$; R′ = R″ = H].

(17) Analogous facile displacements of halogen from 7-halo-4-nitrobenzofurazans have been reported [P. B. Ghosh and M. W. Whitehouse, *J. Med. Chem.*, **11**, 305 (1968)].

(18) N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, **11**, 341 (1946).

(19) N. J. Leonard, W. V. Ruyle, and L. C. Bannister, *ibid.*, **13**, 617 (1948).

(20) N. J. Leonard and W. V. Ruyle, *ibid.*, **13**, 903 (1948).

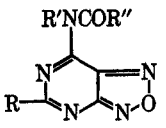
(21) D. J. Brown, *Nature*, **189**, 828 (1961).

(22) J. Goerdeler and W. Roth, *Chem. Ber.*, **96**, 534 (1963).

(23) E. Shaw, *J. Org. Chem.*, **27**, 883 (1962).

TABLE III

7-AMIDOFURAZANO[3,4-*d*]PYRIMIDINES (4)




| R | R′ | R″ | Registry no. | Mp, °C | Recrystn solvent | Calcd (found), % C | H | N | S | Nmr shift (τ) for R | R′ | R″ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | H | H | 30720-45-7 | 122–124 | Ether | 40.23 (40.59) | 2.81 (3.11) | 39.10 (39.15) | | 7.21[a] | | 0.13[a] |
| $CH_3$ | $CH_3$ | H | 30720-46-8 | 95–97 | Ether | 43.52 (43.57) | 3.65 (3.74) | 36.26 (36.59) | | 7.30 | 6.50 | 0.00 |
| $CH_3$ | $C_6H_{11}$ | H | 30720-47-9 | 105–106 | Ether–pentane | 55.16 (55.28) | 5.79 (5.94) | 26.81 (26.98) | | 7.20[a] | 8–9 | 0.75 |
| HNCHO[b] | $CH_3$ | H | 30720-48-0 | 202–204 | Ethanol–acetone | 37.84 (37.91) | 2.72 (2.76) | 37.83 (37.66) | | −0.10 | 6.53 | 0.40[c] |
| $H_2N$[b] | $CH_3$ | H | 30720-49-1 | 285 dec | Aqueous THF | 37.11 (37.15) | 3.11 (3.29) | 43.29 (43.44) | | 0.48 | 6.53 | −1.60 |
| $(CH_3)_2N$ | H | H | 30720-50-4 | 195–196 | Ethanol | 40.38 (40.37) | 3.87 (3.92) | 40.37 (40.27) | | 6.80[d] | −2.16 | 0.46 |
| $(CH_3)_2N$ | $CH_3$ | H | 30720-51-5 | 182–183 | Ethanol | 43.24 (43.11) | 4.54 (4.47) | 37.83 (37.92) | | 6.70[e] | 6.59 | 0.10 |
| $(CH_3)_2N$ | H | $CH_3$ | 30720-52-6 | 211–212 | Ethanol | 43.24 (42.99) | 4.54 (4.62) | 37.83 (37.68) | | 6.82[e] | | 7.67 |
| $(CH_3)_2N$ | $CH_3$ | $CH_3$ | 30720-53-7 | 156–157 | Ethanol | 45.76 (45.65) | 5.12 (5.06) | 35.58 (35.79) | | 6.77 | 6.42 | 7.48 |
| $(CH_3)_2N$ | $CH_3$ | $C_6H_5$ | 30720-54-8 | 122–123 | Ethanol | 56.37 (56.22) | 4.73 (4.86) | 28.18 (28.45) | | 7.18[f] | 6.24 | 2.5 |
| $CH_3S$ | H | H | 30720-55-9 | 173–174 | Ether–pentane | 34.13 (33.97) | 2.39 (2.36) | 33.17 (33.24) | 15.16 (15.29) | 7.41 | | 0.30 |
| $CH_3S$ | $CH_3$ | H | 30720-56-0 | 119–120 | Ether | 37.34 (37.34) | 3.13 (3.27) | 31.11 (31.39) | 14.21 (14.47) | 7.38 | 6.58 | 0.07 |
| $CH_3S$ | $C_2H_5$ | H | 30720-57-1 | 101–102 | Ether–pentane | 40.17 (40.23) | 3.79 (3.89) | 29.28 (29.41) | 13.38 (13.34) | 7.37[a] | 5.72 8.70 | 0.06 |
| $CH_3S$ | $CH_3$ | $C_6H_5$ | 30720-58-2 | 146–148 | Ethanol | 51.82 (51.71) | 3.68 (3.82) | 23.25 (23.23) | 10.64 (10.54) | 7.64 | 6.29 | 2.2–2.7 |
| $C_6H_5$ | $CH_3$ | H | 30720-59-3 | 201–202 | Ethanol–THF | 56.47 (56.56) | 3.55 (3.67) | 27.44 (27.51) | | 1.5–2.4 | 6.40 | 0.03 |
| $C_6H_5$ | H | $CH_3$ | 30720-60-6 | 193 | Ethanol | 56.47 (56.10) | 3.55 (3.48) | 27.44 (27.43) | | 1.3–2.4 | | 7.55 |
| $C_6H_5$ | H | $C_6H_5$ | 30787-98-5 | 185 | Acetone | 64.35 (64.18) | 3.49 (3.39) | 22.07 (21.98) | | | 1.8–2.8 | |
| $C_6H_5$ | $CH_3$ | $CH_3$ | 30720-61-7 | 160 | Ethanol | 57.98 (58.16) | 4.12 (4.10) | 26.01 (26.20) | | 1.7–2.4 | 6.28 | 7.30 |

[a] Spectrum obtained in $CDCl_3$. [b] Formylation of 5-amino-7-methylaminofurazano[3,4-*d*]pyrimidine gave the 5,7-bisformyl derivative only when completely anhydrous media were used in the formylation and purification procedures. Either product may be used in the succeeding step as the 5-*N*-formyl group is hydrolyzed under the reaction conditions. [c] The nmr spectrum of this material also shows a broadened doublet ($J_{AX}$ = 9 Hz at τ −1.6, 1 H, $H_XN_5COH_A$). The resonance at τ −0.10 ($H_A$) is also a broadened doublet ($J_{AX} \cong$ 9 Hz). Upon addition of $D_2O$ the doublet at τ −0.10 collapses to a sharp singlet, and the doublet at τ −1.6 τ is no longer seen. [d] This resonance appears as a doublet ($\Delta\nu$ 4 Hz) due apparently to restricted rotation about the $C_5$–N bond. [e] Somewhat broadened because of restricted rotation. [f] Broadened doublet ($\Delta\nu$ 25 Hz) because of restricted rotation.

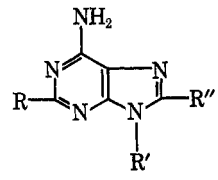
The reductive cleavage of the furazan ring in **4** to give a 4,5-diaminopyrimidine parallels the reductive cleavage of **2** (R = $C_6H_5$) to **7**. However, in the present instance the strongly nucleophilic 5-amino group produced in the reduction reacts rapidly with the ortho-situated acylamino grouping, with consequent ring closure to the adenine. The unusual facility with which imidazole ring formation occurs from **5** is in sharp contrast with the relatively vigorous conditions required for cyclization of 5-acylamino-4,6-diaminopyrimidines, which are the intermediates in the classical Traube conversion of 4,5,6-triaminopyrimidines to adenines.[11,24,25]

We were not able to effect the conversion of 5-unsubstituted 7-aminofurazano[3,4-*d*]pyrimidines (**2**, R = H) to 2-unsubstituted adenines because of the hydrolytic instability of the former compounds (see Experimental Section). However, this apparent limitation was readily circumvented by employing 5-methylthio-7-aminofurazano[3,4-*d*]pyrimidines (**2**, R = $SCH_3$). The resulting 2-methylthioadenines (**6**, R = $SCH_3$) were readily converted to adenines (**6**, R = H) by reductive

(24) The principle of generating a 5-amino group in the presence of a 6-acylamino substituent has previously been utilized by Pfleiderer to effect a mild purine ring closure: F. E. Kempter, H. Rokos, and W. Pfleiderer, *Chem. Ber.*, **103**, 885 (1970).

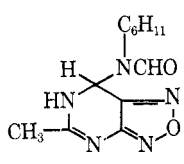
(25) T. Ichikawa, T. Kato, and T. Takenishi [*J. Heterocycl. Chem.*, **2**, 253 (1965)] have described the conversion of 3-aminofurazan-4-carboxamidoxime to adenine by catalytic or chemical reduction in 98% formic acid. On the basis of our present work, a possible sequence of reactions for this overall conversion may be initial reduction of the carboxamidoxime to a carboxamidine grouping, formylation, and then cyclization *in situ* to 7-aminofurazano[3,4-*d*]pyrimidine, a second formylation to **4** (R = R′ = R″ = H), reductive cleavage of the furazan ring, and final cyclization of the resulting **5** (R = R′ = R″ = H) to adenine.

desulfurization.[26] Table IV lists the adenines prepared by step d.

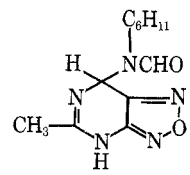


6

A minor reaction pathway which may occur in the reductive cleavage of **4** (step d) was revealed by careful examination of the crude product of either chemical or catalytic reduction of 5-methyl-7-(*N*-formylcyclohexylamino)furazano[3,4-*d*]pyrimidine (**4**, R = $CH_3$; R′ = $C_6H_{11}$; R″ = H). Preparative tlc of the mother liquors from recrystallization of crude **6** (R = $CH_3$; R′ = $C_6H_{11}$; R″ = H) gave a small amount of a by-product. Microanalytical and mass spectral data were strongly suggestive of a dihydro derivative of the furazanopyrimidine. That this material is in fact a mixture of the 6,7- and 4,7-dihydro isomers (tautomers) **12** and **13** be-



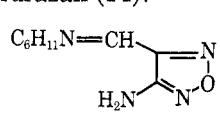
12



13

came clear upon examination of its nmr spectrum. This consisted of what appeared to be two overlapping spectra of unequal intensity, with one displaced slightly from the other such that each peak was an apparent doublet. The $C_5$-methyl protons, the formyl proton, and the N–H proton all appeared as unequal doublets. The cyclohexyl hydrogens appeared as a complex multiplet. The $C_7$ proton also appeared as an unequal doublet, the major component of which was further split into an incompletely resolved doublet ($J \sim 1.5$ Hz). Upon addition of $D_2O$, this latter doublet collapsed to a sharp singlet, while both N–H resonances disappeared as expected. The ratio of the tautomers **12** and **13** in DMSO-$d_6$ solution appears to be ~75:25 based on integration of that $C_7$–H peak which was coupled to the $N_6$ proton.

Confirmation of the chemical structure for this by-product was obtained by hydrolysis with 2 *N* hydrochloric acid to give the cyclohexylamine imine of 3-amino-4-formylfurazan (**14**).



14

7-Aminofurazano[3,4-*d*]pyrimidines (**2**) have proven to be versatile intermediates for the preparation of a variety of other fused pyrimidine heterocycles. For example, displacement of the labile 7-amino grouping can be effected by other nucleophiles such as β-dicarbonyl compounds, acyl hydrazides, and α-amino ketones; subsequent hydrogenolysis of the furazan ring followed by ring closure (analogous to the conversion of **4** to **6**) gives pyrrolo[3,2-*d*]pyrimidines, 7-aza-7,8-dihydropteridines (pyrimido[5,4-*e*]-*as*-triazines), and 7,8-dihydropteridines, respectively. These results will be described in detail in forthcoming publications.

(26) Protection of the 2 position in purines by sulfur substituents during the course of synthetic manipulations elsewhere has seen frequent use.[4,10] Furthermore, the 2-methylthioadenines, here utilized as precursors for adenines, are themselves of biological importance.[27]

(27) S. M. Hecht, N. J. Leonard, W. J. Burrows, D. J. Armstrong, F. Skoog, and J. Occolowitz, *Science*, **166**, 1272 (1969), and references cited therein.

## Experimental Section[28]

**7-Aminofurazano[3,4-*d*]pyrimidines (2). Step a.**—To a suspension of a 4,6-diamino-5-nitrosopyrimidine (**1**) in glacial acetic acid (15 ml/g) was added portionwise with stirring and under $N_2$ a 5% molar excess of lead tetraacetate over a period of 30 min. Stirring was continued overnight and the suspended yellow solid collected by filtration, washed well with water, and recrystallized as indicated in Table I. An additional amount of product could often be obtained by evaporation of the acetic acid filtrate, trituration of the residue with water, filtration, and extraction of the collected solid with the appropriate solvent.

**7-Alkylaminofurazano[3,4-*d*]pyrimidines (3). Step b. Method A.**—The 7-aminofurazano[3,4-*d*]pyrimidine was dissolved or suspended in a large excess of the appropriate amine (*ca.* 1 g/10 ml); a glass pressure vessel was employed for low-boiling amines. The reaction mixture was stirred for several hours, excess amine evaporated under reduced pressure, and the residual solid recrystallized from the appropriate solvent (see Table II). The course of these displacement reactions could readily be followed by tlc using silica gel G and mixtures of ethanol and chloroform as developing solvents. Products could often be readily and conveniently purified by column chromatography employing Florisil as absorbent and mixtures of chloroform and ethanol as eluents. When higher alkylamines (*e.g.*, cyclohexylamine) were employed, it was often possible to extract excess amine with water from a chloroform solution of the reaction mixture.

**Method B.**—Conversion of 7-aminofurazano[3,4-*d*]pyrimidines to 7-alkylaminofurazano[3,4-*d*]pyrimidines could also be carried out conveniently by employing DMF as solvent to which was added a 10% molar excess of the appropriate alkylamine. The product was isolated by extraction of both solvent and excess amine with water from a chloroform solution of the reaction mixture.

**Method C.**—A suspension of the 7-aminofurazano[3,4-*d*]-pyrimidine in 25–40% aqueous alkylamine (1 g/10 ml) was stirred overnight at room temperature, and the suspended solid collected by filtration, washed well with water, and recrystallized from the appropriate solvent (see Table II).

**7-Amidofurazano[3,4-*d*]pyrimidines (4). Step c. Formylation.**—An equimolar mixture of 98% formic acid and acetic anhydride was allowed to stand at 0° for 1 hr, the 7-alkylaminofurazano[3,4-*d*]pyrimidine was added (1 g/20 ml of the above formylating solution), and the reaction mixture was stirred to effect solution and then allowed to stand overnight at room temperature. It was then evaporated *in vacuo* at 40° and the residual solid recrystallized as specified in Table III. Some care was required at this stage because of facile deformylation which was occasionally observed upon attempted recrystallization from ethanolic or aqueous solvents.

**Acylation and Aroylation.**—The above 7-alkylaminofurazano-[3,4-*d*]pyrimidines were readily acetylated by brief warming with acetic anhydride or by dissolution in acetic anhydride or acetyl chloride in pyridine solution. Benzoylation was carried out by treatment with benzyl chloride in pyridine solution. Products were recrystallized as specified in Table III.

**Adenines (6). Step d. Method A.**—A solution of the 7-aminofurazano[3,4-*d*]pyrimidine in glacial acetic acid (1 g/100 ml) was hydrogenated over 10% Pd/C at 50 psi of hydrogen at room temperature until hydrogen uptake ceased. The excess

(28) Microanalyses were performed by Baron Consulting Co., Orange, Conn., and Galbraith Microanalytical Laboratories, Lonsdale, Tenn. Melting points are uncorrected. Nmr spectra were obtained in DMSO-$d_6$ (except where otherwise noted) on a Varian A-60A instrument. Infrared spectra were determined on a Perkin-Elmer 237-B grating spectrometer using KBr disks. Uv spectra were obtained on a Cary Model 11 recording spectrophotometer. Reported yields are of isolated products homogeneous to tlc.

TABLE IV.—ADENINES (6)

| R | R′ | R″ | Registry no.[o] | Method | Yield, % | Mp, °C | Calcd (found), % C | H | N | S | Uv, $\lambda_{max}$,[k] nm (log ε) | Nmr shift (τ) for[l] R | R′ | R″ | Mp, °C[p] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | H | H[a] | | A | 81 | >300 (lit. >350,[b] >300[c] | | | | | | | | | |
| $CH_3$ | $CH_3$ | H[a] | (30720-63-9) | A | 78 | 237–238 (lit.[d] 238) | | | | | See also footnote *e* | | | | 190–192 |
| $CH_3$ | $C_6H_{11}$ | H | 30720-64-0 | A | 90 | 215–216 | 62.31 (62.38) | 7.41 (7.31) | 30.28 (30.49) | | 264 (4.18) | 7.54 | 7.8–8.7 | 1.92 | |
| $H_2N$ | $CH_3$ | H[f] | 30720-65-1 | A | 98 | 314–316 dec | 43.89 (43.87) | 4.91 (4.75) | 51.20 (51.17) | | 216 (4.43), 255 (3.86), 283 (3.97) | 4.18 | 6.47 | 2.40 | |
| $(CH_3)_2N$ | H | H[a] | | A | 64 | 295–296 (lit.[g] 295) | | | | | See also footnote *h* | | | | |
| $(CH_3)_2N$ | H | $CH_3$ | 30720-66-2 | A | 97 | 271–273 | 49.98 (49.77) | 6.29 (6.21) | 43.72 (43.99) | | 226 (4.30), 253 (4.06), 294 (3.89) | 6.95 | | 7.65 | |
| $(CH_3)_2N$ | $CH_3$ | H | 30720-67-3 | A | 77 | 224–225 | 49.98 (49.87) | 6.29 (6.21) | 43.72 (43.73) | | 221 (4.34), 258 (4.02), 295 (3.87) | 6.90 | 6.41 | 2.30 | |
| $(CH_3)_2N$ | $CH_3$ | $CH_3$ | 30720-68-4 (30720-69-5) | A | 78 | 273–274 | 52.41 (52.36) | 6.84 (6.98) | 40.75 (40.47) | | 218 (4.39), 258 (4.09), 296 (3.95) | 6.70[m] | 6.20 | 7.18 | 142–144 |
| $(CH_3)_2N$ | $CH_3$ | $C_6H_5$ | 30720-70-8 | A | 76 | 250–251 | 62.66 (62.78) | 6.02 (6.05) | 31.32 (31.57) | | 230 (4.53), 274 (4.01), 318 (4.24) | 6.92 | 6.37 | 2.0–2.8 | |
| $CH_3S$ | H | H[a] | | A | 91 | 290–292 (lit.[c] 290) | | | | | | | | | |
| $CH_3S$ | $CH_3$ | H[a] | | A | 80 | 263–265 (lit.[c] 262–263) | | | | | | | | | |
| $CH_3S$ | $C_2H_5$ | H | 30720-71-9 | A | 60 | 235–237 | 45.93 (45.87) | 5.30 (5.17) | 33.48 (33.34) | 15.30 (15.19) | 234 (4.34), 278 (4.14) | 7.52 | 5.86 8.54 | 2.04 | |
| | | | | B | 73 | | | | | | | | | | |
| $CH_3S$ | $CH_3$ | $C_6H_5$ | 30720-72-0 | A | 87 | 266–267 | 57.56 (57.49) | 4.83 (4.79) | 25.82 (25.85) | 11.80 (11.65) | 237 (4.46), 302 (4.28) | 7.43 | 6.20 | 2.0–2.5 | |
| H | $C_2H_5$ | H[a] | | *i* | 85 | 195–196 (lit.[j] 194–195) | | | | | | | | | |
| H | $CH_3$ | $C_6H_5$ | 30720-73-1 | *i* | 75 | 224–226 | 63.98 (63.88) | 4.92 (4.94) | 31.09 (31.20) | | 229 (4.30), 282 (4.27) | 1.89 | 6.24 | 2.1–2.7 | |
| $C_6H_5$ | $CH_3$ | H | 30720-74-2 (30720-75-3) | B | 83 | 239–240 | 63.98 (63.90) | 4.92 (4.92) | 31.09 (31.14) | | 238 (4.40), 272 (4.14) | 1.38–2.38 | 6.14[n] | 1.46 | 215 |
| $C_6H_5$ | H | $CH_3$ | 30720-76-4 (30720-77-5) | A | 80 | 280 dec | 63.98 (63.98) | 4.92 (5.01) | 31.09 (30.90) | | 237 (4.41), 275 (4.20) | 1.7–2.6 | | 7.49 | 227–228 |
| | | | | B | 58 | | | | | | | | | | |
| $C_6H_5$ | H | $C_6H_5$ | 30720-78-6 (30720-79-7) | B | 72 | 290–291 | 71.06 (70.89) | 4.56 (4.57) | 24.38 (24.27) | | 242 (4.80), 313 (4.43) | 1.7–2.6 | | 1.7–2.6 | 255 |
| $C_6H_5$ | $CH_3$ | $CH_3$ | 30720-80-0 (30720-81-1) | B | 70 | 245–246 | 65.25 (65.19) | 5.48 (5.36) | 29.27 (29.32) | | 237 (4.41), 275 (4.19) | 1.7–2.6 | 6.33[n] | 7.79 | 185 |

[a] Known compound; its physical properties were in close agreement with those reported. In cases where authentic samples were available, identity was established by comparison of infrared and ultraviolet spectra and mixture melting point determinations. [b] R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Amer. Chem. Soc.*, **75**, 263 (1953). [c] J. Baddiley, B. Lythgoe, D. McNeil, and A. R. Todd, *J. Chem. Soc.*, 383 (1943). [d] J. Baddiley, B. Lythgoe, and A. R. Todd, *ibid.*, 318 (1944). [e] W. Friedrich and K. Bernhauer, *Chem. Ber.*, **90**, 465 (1957). [f] Mentioned in G. B. Elion, G. H. Hitchings, and H. Vanderwerff, *J. Biol. Chem.*, **192**, 505 (1951), but no properties given. [g] K. J. M. Andrews, N. Anand, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 2490 (1949). [h] J. A. Montgomery and L. Holum, *J. Amer. Chem. Soc.*, **80**, 404 (1958). [i] Prepared by Raney nickel desulfurization of the corresponding methylthio derivative (see Experimental Section). The yield quoted is for the desulfurization reaction. [j] J. A. Montgomery and C. Temple, Jr., *J. Amer. Chem. Soc.*, **79**, 5238 (1957). [k] Determined in aqueous solution at pH 7. [l] In addition to those reported below, $H_2N^6$ resonances were observed as broadened singlets at τ 2.5–3.5. [m] Obtained in acidic $D_2O$ solution, using sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standard. [n] Nmr data obtained on $N^6$-acetyl derivative because of difficult solubility of the parent compound. The additional $CH_3CON$ signal appeared at τ 7.5–7.6. [o] Registry no. of the acetate is in parentheses. [p] Of monoacetyl derivative

hydrogen was removed by evacuation and the solution heated at 80° for 2 hr and cooled, the catalyst removed by filtration, and the filtrate evaporated under reduced pressure to dryness. The residual solid was triturated with water and the resulting suspension adjusted to neutrality with dilute aqueous ammonia and filtered. The adenines thus obtained were purified either directly by recrystallization (from water, ethanol, or aqueous ethanol) or by prior column chromatography using Florisil as adsorbent and mixtures of chloroform and ethanol as developing solvents (see Table IV).

**Method B.**—To a solution of the 7-amidofurazano[3,4-*d*]-pyrimidine in glacial acetic acid (1 g/15 ml) was added portionwise, over a period of 30 min, a twofold weight excess of powdered zinc. The reaction mixture was cooled when necessary by use of a water bath. After addition of zinc was complete, the reaction mixture was heated under reflux for 2 hr, cooled, and filtered, and the filtrate evaporated to dryness. The residual solid was triturated with water, collected by filtration, and recrystallized.

**Desulfurization of 2-Methylthioadenines (6, R = $SCH_3$) to Adenines (6, R = H).**—The 2-methylthioadenine was dissolved in aqueous ethanol, a fivefold excess (wt/wt) of Raney nickel (Grace No. 28) added and the reaction mixture refluxed for 3 hr. Filtration of the hot reaction mixture, followed by evaporation of the filtrate and recrystallization of the residue from aqueous ethanol, gave the corresponding 2-unsubstituted adenine (see Table IV).

**2-Phenyl-4,6-diamino-5-acetamidopyrimidine (7).**—To a solution of 1.0 g of 5-phenyl-7-aminofurazano[3,4-*d*]pyrimidine (**2**, R = $C_6H_5$) in 15 ml of glacial acetic acid was added 2.0 g of zinc powder in portions over a period of 30 min. The reaction mixture was then heated under reflux for 1.5 hr and evaporated under reduced pressure, and the residue was washed well with water and then recrystallized from ethanol to give 0.61 g (53%) of colorless crystals, mp 285–286°. This material was identical with a sample of **7** prepared independently by refluxing 2-phenyl-4,5,6-triaminopyrimidine in glacial acetic acid for 30 min.

*Anal.* Calcd for $C_{12}H_{13}N_5O$: C, 59.25; H, 5.39; N, 28.79. Found: C, 59.01; H, 5.41; N, 28.65.

**2-Dimethylamino-4,5-diamino-6-formylaminopyrimidine [5, R = $N(CH_3)_2$; R′ = R″ = H].**—A solution of 1.5 g of 5-dimethylamino-7-formylaminofurazano[3,4-*d*]pyrimidine [**4**, R = $N(CH_3)_2$; R′ = R″ = H] in 100 ml of ethanol was hydrogenated over 10% Pd/C at 50 psi until hydrogen uptake ceased. The reduction mixture was then heated to boiling and filtered to remove catalyst, and the filtrate was concentrated under reduced pressure, cooled, and filtered. The collected solid was recrystallized from ethanol to give 1.1 g (80%) of colorless needles: mp 285–287° dec; nmr $\tau$ 7.0 (6 H, $N(CH_3)_2$), and 3.9 (1 H, CHO) (no change upon addition of $D_2O$); ir 1690 and 1710 $cm^{-1}$.

*Anal.* Calcd for $C_7H_{12}N_6O$: C, 42.85; H, 6.16; N, 42.84. Found: C, 43.08; H, 6.11; N, 43.09.

Acetylation with acetic anhydride at 80–90° for several hours, followed by recrystallization of the crude product from ethanol, gave 2-dimethylamino-4,5,6-tris(acetylamino)pyrimidine, mp 231–232°, identical with an authentic sample prepared by analogous acetylation of 2-dimethylamino-4,5,6-triaminopyrimidine.

*Anal.* Calcd for $C_{12}H_{18}N_6O_3$: C, 48.97; H, 6.17; N, 28.56. Found: C, 49.15; H, 6.15; N, 28.60.

**2-Dimethylaminoadenine [6, R = $N(CH_3)_2$; R′ = R″ = H].**—2-Dimethylamino-4,5-diamino-6-formylaminopyrimidine, prepared as described above, was converted quantitatively to 2-dimethylaminoadenine by dissolution in glacial acetic acid at room temperature. The product was identical with an authentic sample.

**5-Methyl-7-(*N*-formylcyclohexylamino)-6,7- (and -4,7-) dihydrofurazano[3,4-*d*]pyrimidine (12 and 13).**—The mother liquors from recrystallization of crude **6** (R = $CH_3$; R′ = $C_6H_{11}$; R″ = H) (obtained by both methods A and B) were examined by tlc (silica gel G, 10% ethanol in chloroform as developing solvent) and found to contain an additional component. Separation of this component was achieved by preparative tlc (1.5-mm silica gel G plates, four successive developments with 10% ethanol in chloroform). Elution from the plates followed by recrystallization from methanol and chloroform afforded a small amount of colorless prisms: mp 181–182°; *m/e* 263; ir 1660 and 1670 $cm^{-1}$; uv $\lambda_{max}^{pH\ 7}$ 278 nm (log $\epsilon$ 3.86) (*cf.* ref 16); nmr for **12** $\tau$ 7.93 (3 H, $C_5$-$CH_3$), 3.22 ($C_7$-H), 1.70 (1 H, CHO), 1.20 (1 H, $N_6$-H), 8–9 (11 H, multiplet, $C_6H_{11}$), $J_{C_7\text{-}H\text{-}N_6\text{-}H}$ = 1.5 Hz; nmr for **13** $\tau$ 7.86 (3 H, $C_5$-$CH_3$), 3.08 (1 H, $C_7$-H), 1.60 (1 H, CHO), 0.80 (1 H, $N_4$-H), 8–9 (11 H, $C_6H_{11}$).

*Anal.* Calcd for $C_{12}H_{17}N_5O_2$: C, 54.74; H, 6.51; N, 26.60. Found: C, 54.78; H, 6.43; N, 26.86.

Hydrolysis of 150 mg of the mixture of **12** and **13** with 10 ml of 2 *N* hydrochloric acid overnight at steam bath temperatures, followed by neutralization of the reaction mixture with aqueous ammonia, gave a white solid which was collected by filtration and recrystallized from aqueous methanol to give 57 mg (55%), mp 91–92°, of the **cyclohexylamine imine of 3-amino-4-formylfurazan (14)**: *m/e* 194, uv $\lambda_{max}^{H_2O}$ 277 nm (log $\epsilon$ 3.75); nmr $\tau$ 8–9 (11 H, broad multiplet, $C_6H_{11}$), 3.5 (2 H, broad, $NH_2$), 1.28 (1 H, singlet, (HC=N).

*Anal.* Calcd for $C_9H_{14}N_4O$: C, 55.65; H, 7.27; N, 28.85. Found: C, 55.69; H, 7.12; N, 29.01.

**3-(*N*′-Methylformamidino)-4-(*N*-methylcarboxamidino)furazan (10).**—The susceptibility of 5-unsubstituted furazano[3,4-*d*]-pyrmidines to ring cleavage in the presence of nucleophiles is illustrated by the following experiment. A suspension of 1.5 g of 7-aminofurazano[3,4-*d*]pyrimidine (**2**, R = H) in 15 ml of 40% aqueous methylamine was stirred for 1.5 hr at room temperature and diluted with 30 ml of water, and the precipitated solid was collected by filtration, washed with water, and recrystallized from ethanol to give 1.78 g (90%) of **10**: mp 165–166° as colorless crystals; *m/e* 182 ($CH_3N$=$CHNH^+$, 57); uv $\lambda_{max}^{C_2H_5OH}$ 246, 287 (sh) nm (log $\epsilon$ 4.17, 3.80); nmr $\tau$ 7.34, 7.24 (each 3 H, $NCH_3$), 1.84 (1 H, NCH=N), 2.64 (2 H, broad, $NH_2$).

*Anal.* Calcd for $C_6H_{10}N_6O$: C, 39.55; H, 5.53; N, 46.13. Found: C, 39.25; H, 5.27; N, 45.63.

**10** was formed analogously from 7-methylaminofurazano-[3,4-*d*]pyrimidine (**3**, R = H; R′ = $CH_3$) by treatment with methylamine under the same conditions as described above.

More vigorous treatment of either 7-amino- or 7-methylaminofurazano[3,4-*d*]pyrimidine with 40% aqueous methylamine (48 hr at room temperature) resulted in further hydrolysis of the initially formed **10** to give **3-amino-4-(*N*-methylcarboxamido)furazan (11)**: mp 202° (from ethanol); uv $\lambda_{max}^{C_2H_5OH}$ 233, 285 nm (log $\epsilon$ 3.35, 3.39); nmr $\tau$ 7.20 (3 H, doublet, $J$ = 3 Hz, $NHCH_3$), 3.60 (2 H, broad, $NH_2$), 1.0 (1 H, $NHCH_3$).

*Anal.* Calcd for $C_4H_6N_4O_2$: C, 33.81; H, 4.27; N, 39.43. Found: C, 33.85; H, 4.12; N, 39.41.

**7-Methylaminofurazano[3,4-*d*]pyrimidine (3, R = H; R′ = $CH_3$).**—Compound **10** could be converted to 7-methylaminofurazano[3,4-*d*]pyrimidine by heating in the absence of a solvent at 170–180°. Recrystallization of the solidified fusion product from ethanol gave light yellow crystals: mp 237–238°; uv $\lambda_{max}^{C_2H_5OH}$ 213, 364 nm (log $\epsilon$ 4.12, 3.90); nmr $\tau$ 7.03 (3 H, $NCH_3$), 1.65 (1 H, $C_5$-H), 0.15 (1 H, broad, NH).

*Anal.* Calcd for $C_5H_5N_5O$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.83; H, 3.29; N, 46.60.

**Acid Hydrolysis of 7-Aminofurazano[3,4-*d*]pyrimidine (2, R = H). Formation of 3-Amino-4-carboxamidinofurazan.**—The susceptibility of 5-unsubstituted furazano[3,4-*d*]pyrimidines to acid hydrolysis is illustrated by the following conversion. A solution of 0.5 g of 7-aminofurazano[3,4-*d*]pyrimidine (**2**, R = H) in 5 ml of 5 *N* hydrochloric acid was allowed to stand at room temperature for 1 hr and concentrated to dryness *in vacuo* at <20°, and the residue was recrystallized from ethanol–diethyl ether to give 3-amino-4-carboxamidinofurazan hydrochloride, mp 200°, as colorless crystals: uv $\lambda_{max}^{C_2H_5OH}$ 282 nm (log $\epsilon$ 3.20); nmr $\tau$ 3.22 (2 H, broad, $NH_2$), −0.06 (4 H, broad, $C(=NH_2)NH_2^+$).

*Anal.* Calcd for $C_3H_5N_5O\cdot HCl$: C, 22.09; H, 3.67; N, 42.88. Found: C, 21.98; H, 3.56; N, 42.87.

By contrast, 5-phenyl-7-aminofurazano[3,4-*d*]pyrimidine (**2**, R = $C_6H_5$) was recovered unchanged after treatment under the same conditions. More vigorous conditions resulted in hydrolysis of the 7-amino grouping with the formation of **5-phenyl-7(6*H*)-furazano[3,4-*d*]pyrimidinone**, obtained as colorless crystals, mp 223–224°, upon recrystallization from ethanol.

*Anal.* Calcd for $C_{10}H_6N_4O_2$: C, 56.07; H, 2.82; N, 26.10. Found: C, 56.22; H, 3.04; N, 26.08.

**Registry No.**—**3** (R = H; R′ = $CH_3$), 30720-44-6; **5** [R = $N(CH_3)_2$; R′ = R″ = H], 30720-62-8; **7**, 30720-82-2; **10**, 30720-83-3; **11**, 30720-84-4; **12**, 30787-99-6; **13**, 30787-99-6; **14**, 30724-62-0; 2-dimethylamino-4,5,6-tris(acetylamino)pyrimidine, 30724-63-1; 3-amino-4-carboxamidinofurazan HCl, 30724-64-2; 5-phenyl-7(6*H*)-furazano[3,4-*d*]pyrimidinone, 30724-65-3.