(m, H_8) ($J_{5,6}$ = 8.4, $J_{6,7}$ = 6.9, $J_{7,8}$ = 8.0, $J_{5,7}$ = 1.2, $J_{6,8}$ = 1.6, $J_{5,8}$ = 0.6, $J_{1,5}$ = 0.6 Hz).

Anal. Calcd for $C_9H_5BrN_4$ (mol wt 249.09): C, 43.40; H, 2.02; Br, 32.08. Found: C, 43.19; H, 2.31; Br, 31.67.

Preparation of 2,3-Diaminoisoquinolinium Salts 10-12. A solution of the requisite 3-aminoisoquinoline derivative (5.0 mmol) in 10 mL of dichloromethane was treated with a solution of 5.2 mmol of *O*-tosylhydroxylamine in 20 mL of dichloromethane at 0-5 °C. The product precipitated in crystalline form within 10 min. A further quantity of the crystals deposited on addition of a limited amount ot ether. Recrystallization from isopropyl alcohol gave rise to brilliant yellow needles.

2,3-Diaminoisoquinolinium tosylate (10): mp 160-162 °C (65%); perchlorate salt, mp 170-172 °C; NMR (TFA) δ 9.1 (s, 1 H, H_1), 8.0-7.5 (m, 4 H, H_{5-8}), 8.45 (s, 1 H, H_4).

Anal. Calcd for $C_{16}H_{17}N_3O_3S$ (mol wt 331.40): C, 57.99; H, 5.17; S, 9.68. Found: C, 57.70; H, 5.40; S, 9.61.

2,3-Diamino-4-methylisoquinolinium tosylate (12): mp 168-170 °C (67%); fluoroborate salt, mp 182-184 °C; NMR (TFA) δ 9.1 (s, 1 H, H_1), 8.05-7.4 (m, 4 H, H_{5-8}), 2.65 (s, 3 H, CH_3).

Anal. Calcd for $C_{17}H_{19}N_3O_3S$ (mol wt 345.43): C, 59.11; H, 5.54; S, 9.28. Found: C, 58.93; H, 5.80; S, 9.03.

1-Bromo-2,3-diaminoisoquinolinium tosylate (11): mp 175-177 °C (45%).

Anal. Calcd for $C_{16}H_{16}BrN_3O_3S$ (mol wt 410.31): C, 46.84; H, 3.93; N, 10.24; Br, 19.48. Found: C, 46.52; H, 3.98; N, 10.01; Br, 19.10.

Reaction of the Diaminoisoquinolinium Salts with Nitrous Acid. A solution of the 2,3-diaminoisoquinolinium derivative (3.0 mmol) in a mixture of 10 mL of acetic acid and 10 mL of water was treated with a solution of 0.35 g (5.1 mmol) of sodium nitrite in 3 mL of water at room temperature. Cryatalline precipitate deposited within few minutes which was filtered and recrystallized from the given solvent.

Tetrazolo[1,5-*b*]isoquinoline (1a). The product obtained by this procedure in 70% yield proved to be fully identical (spectroscopical data and physical constants) with that prepared by earlier methods.[1,2]

10-Methyltetrazolo[1,5-*b*]isoquinoline (14): mp 139-141 °C (EtOH); yield 65%.

Anal. Calcd for $C_{10}H_8N_4$ (mol wt 184.21): C, 65.20; H, 4.38; N, 30.42. Found: C, 64.92; H, 4.51; N, 30.18.

3-Azido-1-bromoisoquinoline (13): mp 113-114 °C (MeOH); yield 60%.

Anal. Calcd for $C_9H_5BrN_4$ (mol wt 249.09): C, 43.40; H, 2.02; Br, 32.08. Found: C, 43.28; H, 2.34; Br, 31.72.

10-Methyltetrazolo[1,5-*b*]isoquinoline HBF_4 Salt (14c). A solution of **14** in TFA was treated with a few drops of hydrofluoroboric acid (40%) and ether was added. Colorless crystals separated which were recrystallized from nitromethane; mp 174-175 °C.

Anal. Calcd for $C_{10}H_9BF_4N_4$ (mol wt 272.03): C, 44.15; H, 3.83; N, 20.60. Found: C, 43.87; H, 3.95; N, 20.31.

Registry No. **1a**, 33459-64-2; **1b**, 60877-39-6; **2**, 15787-12-9; **3**, 75949-08-5; **4**, 75949-09-6; **5**, 75949-10-9; **6a**, 75949-11-0; **6b**, 75949-12-1; **7**, 25475-67-6; **8**, 13130-79-5; **9**, 7697-66-7; **10**, 75949-14-3; **10** perchlorate salt, 75949-15-4; **11**, 75949-17-6; **12**, 75949-19-8; **12** fluoroborate salt, 75949-20-1; **13**, 75949-21-2; **14a**, 75949-22-3; **14b**, 75949-23-4; **14c**, 75949-25-6; **15a**, 75949-26-7; **15b**, 75961-48-7.

Pyrimidines. 17. Novel Pyrimidine to Pyridine Transformation Reaction. One-Step Synthesis of Pyrido[2,3-*d*]pyrimidines[1]

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A number of 2,6-dihydroxypyridines (**3**) and pyrido[2,3-*d*]pyrimidines (**9**) were prepared in one step from 1,3-dimethyluracil derivatives (**1**) via new transfragment reactions by which the N_1-C_2-N_3 fragment of **1** is displaced by the C-C-N fragment of acyclic or cyclic 1,3-ambident nucleophiles. As acyclic nucleophiles, acetamide derivatives (**2**) substituted at the α position with an electron-withdrawing R^3 group were employed. The products were 2,6-dihydroxypyridines substituted at C_3 with R^3 (**3**). 1,3-Dimethyl-4-thiouracil (**4**) could be converted into 2-hydroxy-6-mercaptonicotinamide (**5**) by treatment with malonamide. 1-Methylpyridine derivatives (**6**) could be obtained by treatment of 1,3-dimethyluracil (**1a**) with *N,N'*-dimethylmalonamide or *N*-methylcyanoacetamide. Treatment of **1a** with malononitrile in ethanolic NaOEt gave 3-cyano-2-ethoxy-6-hydroxypyridine (**7**). Derivatives of 1,3-dialkyl-6-aminouracil (**8**) were used as cyclic 1,3-ambident nucleophiles. Treatment of 5-substituted 1,3-dimethyluracil (**1**) with **8** in base afforded 1,3-dialkyl-6-substituted-pyrido[2,3-*d*]pyrimidine-2,4,7-(1*H*,3*H*,8*H*)-trione (**9**). Compound **4** was converted into 7-mercapto-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**10**) by treatment with 1,3-dimethyl-6-aminouracil. Treatment of 5-cyano-1,3-dimethyluracil (**1g**) with 1-*n*-butyl-6-aminouracil (**11**) afforded 1-*n*-butyl-6-cyanopyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**12**). Plausible mechanisms for the pyrimidine-to-pyridine and pyrimidine-to-pyrido[2,3-*d*]pyrimidine transformation reactions are proposed.

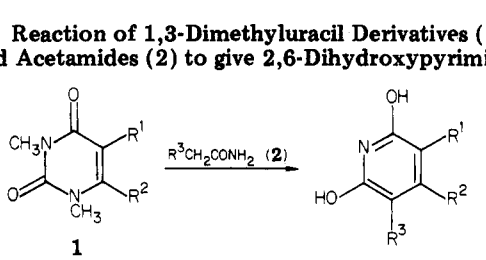
The synthesis of simple heterocyclic compounds has been approached in three different ways: (a) total synthesis by cyclization of acyclic compounds, (b) introduction or modification of functional groups on a heterocyclic ring, and (c) ring transformations of cyclic compounds.[2] For preparative purposes, the last method has rarely been employed. For example, uracil derivatives were converted into pyrazolone by treatment with hydrazine;[3] however,

(1) This investigation was supported by funds from the National Cancer Institute, U.S. Department of Health and Human Services Grants No. CA-08748 and CA-18601.

(2) For a comprehensive review of ring transformations, see: van der Plas, H. C. "Ring transformations of Heterocycles"; Academic Press: London and New York, 1973; Vol. 1 and 2.

0022-3263/81/1946-0846$01.00/0

Table I. Reaction of 1,3-Dimethyluracil Derivatives (1) with Substituted Acetamides (2) to give 2,6-Dihydroxypyrimidines (3)



1 3

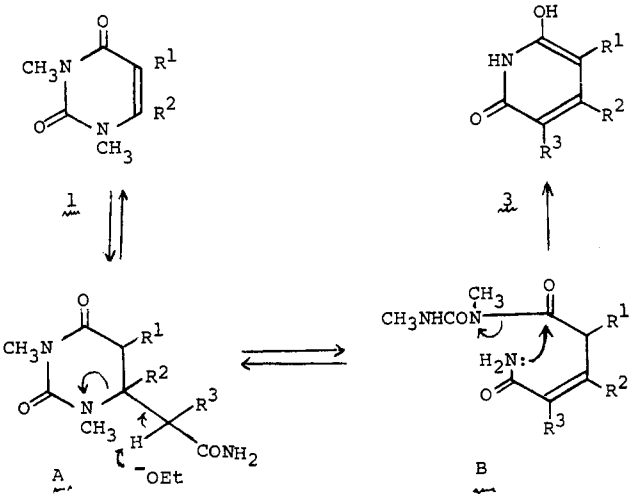
	R¹	R²	R³	molar ratio of 1/2 NaOEt	reaction time, min	yield, %	crystallizn solv
3a	H	H	$CONH_2$	1:4:4	20	80	H_2O
3b	CH_3	H	$CONH_2$	1:4:4	180	65	AcOH
3c	H	CH_3	$CONH_2$	1:4:4	360	0[a]	
3d	F	H	$CONH_2$	1:4:4	10	38[b]	EtOH
3e	Cl	H	$CONH_2$	1:4:4	20	95[c]	EtOH
3f	Br	H	$CONH_2$	1:4:4	30[d]	67[e]	DMF-H_2O
3g	CN	H	$CONH_2$	1:4:4	10	68	H_2O
3h	NO_2	H	$CONH_2$	1:4:4	10	0[f]	
3i	H	H	CN	1:4:4	30	97	H_2O
3j	H	H	$COCH_3$	1:4:4	300	51	H_2O
3k	H	H	C_6H_5	1:1:1	420	30	EtOH
3m	H	H	COONa	1:4:8	1440	14	H_2O

[a] No reaction. Recovery of 1c. [b] Considerable loss due to decomposition during recrystallization. [c] Recrystallization not possible. Washed with boiling EtOH. [d] Room temperature. [e] Analytically pure product not obtained. [f] Adduct formation.

this reaction has been little explored for its synthetic utility but was later used for other purposes, such as the preparation of apyrimidinic acids from nucleic acids.[4]

Recently, we discovered[5] a new and practical pyrimidine-to-pyrimidine transformation reaction by which the N_1–C_2–N_3 fragment of the pyrimidine ring is directly replaced by an ambident N–C–N fragment. Thus, variously substituted 1,3-dialkyluracils (1) were converted smoothly into substituted isocytosine, 2-thiouracil, or uracil derivatives by an intermolecular transfragment reaction[6-9] upon treatment with guanidine, thiourea, or urea, respectively. This reaction became very important in large-scale preparations of ψ-isocytidine from ψ-uridine. ψ-Isocytidine is a potential antileukemic agent[10,11] originally synthesized in our laboratory.[12] Oostveen et al.[9] reported the coversion of 1-methylpyrimidinium iodide into 2-phenylpyrimidine and 2-*tert*-butylpyrimidine by treatment with benzamidine or pivalamidine. In the above instances, the ambident

Scheme I



nucleophiles contain two nitrogens at their nucleophilic centers. The ease with which this reaction occurred prompted us to explore the preparation of ring systems other than pyrimidine via this general methodology using acyclic or cyclic ambident nucleophiles containing atoms other than nitrogen at one of the nucleophilic centers. This report describes the transformation of the pyrimidine ring into the pyridine system via direct displacement of the N_1–C_2–N_3 portion by acyclic ambident nucleophiles containing a C–C–N fragment. We also describe herein the one-step preparation of the pyrido[2,3-*d*]pyrimidine system from 1 by reaction with cyclic ambident nucleophiles. Preliminary accounts of these subjects have appeared.[13,14]

Treatment of 1,3-dimethyluracil (**1a**) with 4 molar equiv each of malonamide (**2**, $R^3 = CONH_2$) and sodium ethoxide in ethanol at reflux for 30 min, followed by neutralization of the reaction mixture, afforded the known[15] 2,6-dihydroxynicotinamide (**3a**) and 1,3-dimethylurea (Table I).

(3) Fosse, R.; Hieulle, A.; Bass, L. W. *C. R. Hebd. Seances, Acad. Sci.* **1924**, *178*, 811. Levene, P. A.; Bass, L. W. *J. Biol. Chem.* **1926**, *71*, 167. Wamhoff, H.; Wald, K. *Chem. Ber.* **1977**, *110*, 1716.

(4) Takemura, S. *Biochim. Biophys. Acta* **1958**, *29*, 447; *Bull. Chem. Soc. Jpn.* **1959**, *32*, 926. Habermann, A. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3147; *Biochim. Biophys. Acta* **1962**, *55*, 999. Werwoerd, D. W.; Zillig, W. *Ibid.* **1963**, *68*, 48. Temperli, A.; Turler, H.; Rust, P.; Danon, A.; Chargaff, E. *Ibid.* **1964**, *91*, 462. Ellery, B. W.; Simmons, R. H. *Nature (London)* **1966**, *210*, 1159. Cashmore, A. R.; Peterson, G. B. *Biochim. Biophys. Acta* **1969**, *174*, 591.

(5) Hirota, K.; Watanabe, K. A.; Fox, J. J. *J. Heterocycl. Chem.* **1977**, *14*, 537; *J. Org. Chem.* **1978**, *43*, 1193.

(6) This terminology indicates the nature of our ring transformation more precisely and distinguishes it from intramolecular rearrangements, such as the Dimroth reaction[7] or photochemical transposition reactions.[8] The pyrimidine-to-pyrimidine transformation reactions reported by Oostveen et al.,[9] in which the two-atom fragment (N_1–C_2) or the three-atom fragment (N_1–C_2–N_3) is replaced by an N–C or N–C–N fragment of the reagents, are considered intermolecular transfragment reactions.

(7) Brown, D. J. "Mechanisms of Molecular Migrations"; Thagatajan, B. S., Ed.; Interscience: New York, 1968; Vol. 1, p 209.

(8) Singh, B.; Ullman, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 6911.

(9) Oostveen, E. A.; van der Plas, H. C.; Jongejan, H. *Recl. Trav. Chim. Pays-Bas* **1967**, *95*, 209.

(10) Burchenal, J. H.; Ciovacco, K.; Kalahar, K.; O'Toole, T.; Kiefner, R.; Dowling, M. D.; Chu, C. K.; Watanabe, K. A.; Wempen, I.; Fox, J. J. *Cancer Res.* **1976**, *36*, 1520.

(11) Chou, T.-C.; Burchenal, J. H.; Fox, J. J.; Watanabe, K. A.; Chu, C. K.; Philips, F. S. *Cancer Res.* **1979**, *39*, 720.

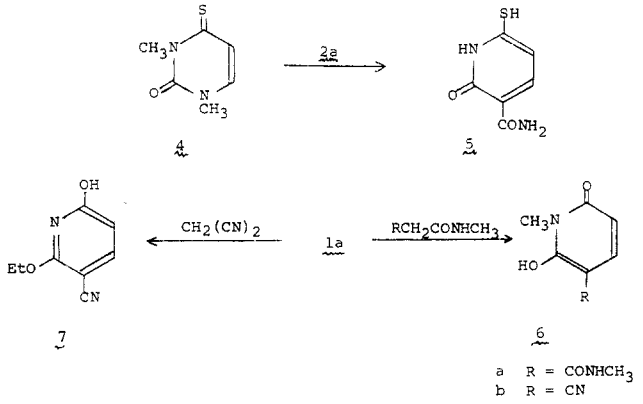
(12) Chu, CK.; Wempen, I.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1976**, *41*, 2793.

(13) Hirota, K.; Kitade, Y.; Senda, S.; Halat, M. J.; Watanabe, K. A.; Fox, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 4423.

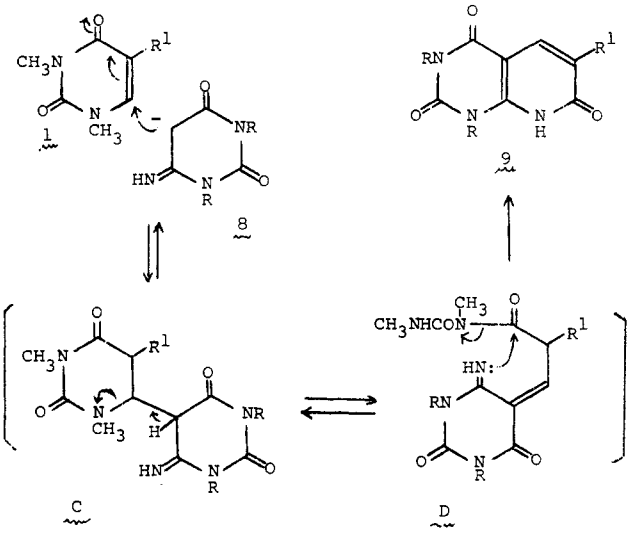
(14) Hirota, K.; Kitade, Y.; Senda, S. *Heterocycles* **1980**, *14*, 407.

(15) Guthzeit, M.; Laska, L. *J. Prakt. Chem.* **1898**, *58*, 403.

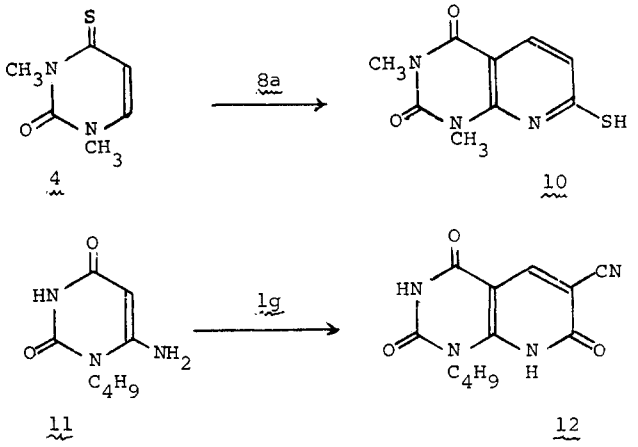
Scheme II



Scheme III



Scheme IV



The former **3a** was further converted into 2,6-dihydroxypyridine[16] by hydrolytic decarboxylation. A plausible mechanism for this transformation was offered via postulated intermediates A and B (Scheme I). The fact that no 2,4-dihydroxynicotinamide was detected in the reaction mixture ruled out the attack of the carbanion on C_4 of **1a**. The effects of C_5 and C_6 substituents also lend support to this mechanism. Thus, a 1,3-dimethyluracil with a C_5 electron-withdrawing group (**1d–g**) was converted into the corresponding 5-substituted 2,6-dihydroxynicotinamide (**3d–g**)[17] rather rapidly upon treatment with malonamide (see Table I), whereas the transformation of 1,3-dimethylthymine (**1b**) into 2,6-dihydroxy-5-methylnicotinamide (**3b**) required a longer reaction time. 1,3,6-Trimethyluracil (**1c**) was recovered almost quantitatively from the attempted reaction with malonamide. The 5-nitro derivaive **1h** did not afford 2,6-dihydroxy-5-nitronicotinamide but gave a Michael adduct. Oostveen and van der Plas[18] reported the transformation of the quaternary pyrimidinium salts into pyridine derivatives by treatment with active methylene compounds. The mechanism proposed for their reaction is similar to the mechanism described herein for the transformation of 1 into **3**.

We also examined the suitability of acetamide derivatives **2** as ambident nucleophiles. Acetamide failed to react with **1a**, probably because carbanion formation is not possible under these reaction conditions. However, acetamide derivatives bearing an electron-withdrawing R^3 group did react with **1a** to afford the 3-substituted 2,6-dihydroxypyridines (**3i–m**, Table I). 2,6-Dihydroxynicotinic acid (**3m**) has been reported as an acid-labile metabolite of nicotinic acid produced by a *Bacillus* species[19,20] and also as a weak inhibitor of fatty acid biosynthesis,[21] but the chemical synthesis of **3m** has not appeared in the literature.

The reaction of 1,3-dimethyl-4-thiouracil (**4**) with malonamide proceeded smoothly to give 2-hydroxy-6-mercaptonicotinamide (**5**) in 83% yield (Scheme II), while treatment of **1a** with *N,N'*-dimethylmalonamide or *N*-methylcyanoacetamide afforded the corresponding 1-methylpyridone derivative **6**. On the other hand, reaction of **1a** with malononitrile in ethanolic sodium ethoxide afforded 2-ethoxy-3-cyano-6-hydroxypyridine (**7**) in 43% yield. Obviously, the solvent participated in this reaction.

In the above reactions, the ambident nucleophiles are acyclic. We have also investigated the feasibility of using cyclic ambident nucleophiles and found that they can replace the N_1–C_2–N_3 fragment of **1**, yielding the corresponding bicyclic products. Thus, 1,3-dimethyl-6-aminouracil (**8a**, Table II), a cyclic 1,3-ambident nucleophile, reacts with 1,3-dimethyluracil (**1a**) in ethanolic sodium ethoxide solution to give 1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,3,7(1*H*,3*H*,8*H*)-trione (**9a**). The bicyclic product **9a** was identical with an authentic sample prepared by the procedure of Broom et al.[24] The proposed mechanism[14] for this bicyclic ring formation involves two intermediates, C and D (Scheme III), and is closely related to the mechanism of the pyrimidine-to-pyridine transformation.[13] The isolation of 7-oxopyridopyrimidine **9a** and not the isomeric 5-oxopyridopyrimidine established that the cyclic carbanion of **8a** (not the exocyclic amino group) attacked the C_6 position of **1a**. As expected, uracil derivatives **1** bearing a C_5 electron-withdrawing group were converted into the corresponding pyridopyrimidines **9** more readily than 1,3-dimethyluracil (**1a**, see Table II). 1,3-Di-

(16) Katritzki et al. reported (*J. Chem. Soc. B* **1966**, 566) that this compound exists in water as a mixture of 60% 6-hydroxy-1*H*-pyridin-2-one, 25% dihydroxypyrdine, and 15% 1*H*,3*H*-pyridin-2,6-dione.

(17) It should be noted that though the products IV are given in the 6-hydroxy-1*H*-pyridin-2-one form, these do not necessarily represent the true tautomeric structures.

(18) Oostveen, E. A.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 233.

(19) Ensign, J. C.; Rittenberg, S. C. *J. Biol. Chem.* **1964**, *239*, 2285.

(20) Hirschberg, R.; Ensign, J. C. *J. Bacteriol.* **1971**, *108*, 757.

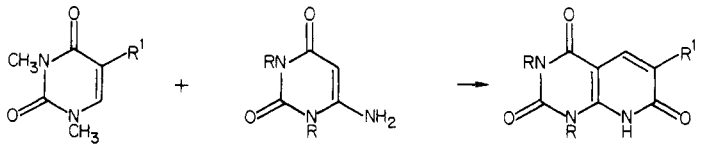
(21) Sunthanker, S. V.; Vaidya, S. D. *Indian J. Chem.* **1973**, *11*, 1315.

(22) This compound was reported in the literature (Johary, N. S.; Kaushal, R. *Vikram* **1960**, *4*, 93; *Chem. Abstr.* **1963**, *58*, 6676a), but its physical constants are not available.

(23) Chase, B. H.; Walker, J. *J. Chem. Soc.* **1953**, 3548.

(24) Broom, A. D.; Shim, J. L.; Anderson, G. L. *J. Org. Chem.* **1976**, *41*, 1095.

Table II. Formation of Pyrido[2,3-*d*]pyrimidines (9)



1a, R^1 = H
g, R^1 = CN
h, R^1 = NO_2
n, R^1 = $COCH_3$
o, R^1 = $CONH_2$

8a, R = CH_3
p, R = CH_2CH_3
q, R = $CH_2CH_2CH_3$

9

starting matl	molar ratio of 1/8/base	reaction time,[a] h	product	R	R^1	yield,[a] %	crystallizn solv
1a + 8a	3:10:20	95	9a	CH_3	H	33	MeOH
1g + 8a	3:10:20	5 (4)	9g	CH_3	CN	52 (63)	H_2O
1h + 8a	3:10:10	3 (3)	9h	CH_3	NO_2	34 (50)	H_2O
1n + 8a	3:10:20	(9)	9n	CH_3	$COCH_3$	(65)	EtOH
1o + 8a	3:10:10	2 (4)	9o	CH_3	$CONH_2$	16 (30)	AcOH
1g + 8p	3:10:20	1	9x	C_2H_5	CN	65	H_2O
1n + 8p	3:10:20	1 (2)	9y	C_2H_5	$COCH_3$	89 (82)	EtOH
1g + 8q	3:10:20	2	9z	C_3H_7	CN	63	EtOH

[a] When KOH instead of NaOEt was used as the base, the reaction time and yield are given in parentheses.

methylthymine (**1b**) was recovered quantitatively from the reaction with **8a**. It should be noted that although the reaction of 1,3-dimethyl-5-nitrouracil (**1h**) with guanidine[5] or malonamide gave the corresponding Michael adduct, reaction of **1h** with **8a** afforded the 6-nitropyridopyrimidine **9h**. The reaction of 5-acetyl-1,3-dimethyluracil (**1n**) with **8a** under the same conditions did not give the expected transformation product **9n**. We found, however, that the use of potassium hydroxide instead of sodium ethoxide gave the desired bicyclic product **9n** in 65% yield. In general, the use of potassium hydroxide somewhat improved the yield of the bicyclic product. The reaction of 1,3-dimethyl-4-thiouracil (**4**) with **8a** in ethanolic sodium ethoxide gave the 7-mercaptopyrido[2,3-*d*]pyrimidine derivative (**10**) in 78% yield (Scheme IV). It was also found that 6-amino-1-*n*-butyluracil (**11**) reacts with **1g** to afford 1-butyl-6-cyanopyrido[2,3-*d*]pyrimidine-2,3,7-(1*H*,3*H*,8*H*)-trione (**12**).

The simple transformation of a uracil to a pyridine or pyridopyrimidine system reported herein represents a new synthetic method of significant potential, especially since several 2,6-dihydroxypyridine[25] and pyridopyrimidine[26] derivatives have shown interesting biological activities.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were obtained on a JEOL J1M-PFT-100 spectrometer, and except when otherwise specified, Me_2SO-d_6 was used as the solvent with Me_4Si as the internal standard; chemical shifts are reported as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet); and *J* values are first order. Microanalyses were performed by Galbraith Laboratories, Inc., and Microanalytical Laboratory, Gifu College of Pharmacy, Gifu, Japan.

2,6-Dihydroxynicotinamide (3a). A mixture of 1,3-dimethyluracil (**1a**; 1.40 g, 0.01 mol) and malonamide (**2a**; 4.5 g, 0.04 mol) in ethanolic sodium ethoxide [prepared by dissolving metallic Na (920 mg, 0.04 mol) in 40 mL of EtOH] was heated at reflux for 20 min. The solvent was removed in vacuo, and the residue was dissolved in cold water (20 mL). Upon acidification with concentrated HCl to pH ~2, the crystalline product precipitated and was collected by filtration. One crystallization from H_2O gave analytically pure **3a**, 1.22 g (80%). For physical constants, see Table III.

The 2,6-dihydroxypyridine derivatives **3** listed in Table I were prepared similarly under the conditions specified in Table III. Compounds **5** and **6** were also prepared in a similar manner (Table III).

2-Ethoxy-3-cyano-6-hydroxypyridine (7). A solution of **1a** (3.5 g, 0.025 mol) and malononitrile (6.6 g, 0.1 mol) in ethanolic sodium ethoxide (2.3 g of Na in 200 mL of EtOH) was heated at reflux for 20 h. The mixture was concentrated to dryness in vacuo, and the solid residue was dissolved in CH_2Cl_2 (100 mL). The solution was washed with H_2O (2 × 100 mL), dried (Na_2SO_4), and concentrated to dryness in vacuo. The solid residue was crystallized from Et_2O–petroleum ether to give 1.77 g (43%) of light beige crystals, mp 115–116 °C. For the physical data for **7** see Table III.

1,3-Dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (9a). Compound **8a** (1.16 g, 7.5 mmol) was dissolved in ethanolic sodium ethoxide [prepared by dissolving metallic Na (345 mg, 15 mmol) in 45 mL of EtOH] and heated at reflux for 1 h. The solution was treated with **1a** (1.05 g, 7.5 mmol), and the mixture was heated at reflux for 95 h. When the mixture cooled to room temperature, insoluble precipitates were removed from the mixture by filtration. The filtrate was concentrated in vacuo, the residue dissolved in cold water (20 mL), and the solution acidified with concentrated HCl to pH 2. The crystalline precipitates were collected by filtration and recrystallized from MeOH to give 510 mg (33%) of **9a**. For physical constants, see Table IV.

6-Cyano-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4,7-(1*H*,3*H*,8*H*)-trione (9g). A mixture of **1g** (500 mg, 0.003 mol) and **8a** (1.65 g, 0.01 mol) in 0.5 M sodium ethoxide in ethanol (40 mL) was heated at reflux for 5 h. The solvent was removed in vacuo, the residue was dissolved in water (20 mL), the insoluble materials were filtered, and the filtrate was acidified with concentrated HCl to pH 2. The crystalline precipitates were collected and recrystallized from water to give analytically pure **9g**. For physical and analytical data, see Table IV.

The pyrido[2,3-*d*]pyrimidine derivatives (**9**) listed in Table II were prepared in a similar manner under the conditions specified in the table.

1,3-Dimethyl-7-mercaptopyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (10). A mixture of **4** (480 mg, 0.003 mol) and **8a** (1.55 g, 0.01 mol) in 0.4 M ethanolic sodium ethoxide (50 mL) was heated at reflux for 24 h and then concentrated to dryness in vacuo. The residue was triturated with water (20 mL), and insoluble materials were removed by filtration. The filtrate was acidified to pH 2 with concentrated HCl. The crystalline pre-

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Table III. Some Physical Constants of 3-Substituted 2,6-Dihydroxypyridine Derivatives (3) and Related Compounds (5-7)[g]

		UV data				^{1}H NMR (Me_2SO-d_6)				
compd	mp, °C	λ_{max}, nm	$10^3\epsilon$	λ_{min}, nm	$10^3\epsilon$	δ(H-4)	δ(H-5)	$J_{4,5}$, Hz	δ(dissociable H)	δ(other)
3a	261-271[a]	326	21.6	285	2.4	7.91 d	5.70 d	8.9	11.0 br s	
		264	9.9	233	1.7					
3b	>300	332	7.6	295	2.7	7.74[b]				1.91 d[b] (CCH_3)
		256	8.4	230	3.8					
3d	>300	336	16.1	288	2.0	7.88 d[c]				
		265	7.7	235	1.8					
3e	225-230[d]	340	19.1	292	1.5	8.17 s				
		268	9.3	238	2.4					
3f	255-260[a]	338	18.4	292	1.8	8.36 s				
		266	9.1	235	2.4					
3g	>300	332	23.7	287	1.3	8.02 s			3.36, 6.74	
		268	14.7	238	2.6				8.66, 10.26	
		217	10.7							
3i	>300	324	19.4	280	1.4	7.82 d	5.68 d	8.1	11.8 br s (2 H)	
		257	12.2	223	1.6					
3j	243-246	339	22.1	291	3.8	7.76 d	5.38 d	9.6		2.37 s (OCH_3)
		274	7.1	246	1.8					
3k	225-227	337	13.3	301	3.6	7.54 d	5.73 d	7.9		7.1-7.8 m (C_6H_5)
		275	6.1	246	3.1					
3m	244-245[a,e]	324	19.6	283	2.8	7.59 d	5.29 d	9.0	3.41 (3 H), 10.38	
		263	10.0	230	1.2					
5	246-247	371	21.6	301	0.9	7.77 d	6.61 d	9.0	9.7 (4 H)	
		273	11.6	241	3.8					
6a	191-194[f]	325	20.3	286	2.6	7.91 d	5.83 d	9.0		2.83 s, 3.30 s (NCH_3)
		267	8.5	239	2.2					
6b	266-267[a,f]	323	17.7	282	1.8	7.76 d	5.70 d	8.7	8.04	
		259	10.9	231	2.5					
7	115-116	292	11.2	272	5.8	7.97 d	6.32 d	8.4	12.0	1.34 t (CH_2CH_3)
		263	6.5	218	3.5					4.39 q (CH_2CH_3)
		245	10.2							

[a] Decomposition. [b] Allylic coupling, 2 Hz. [c] $J_{4,F}$ = 12.2 Hz. [d] Signals attributed to impurities at δ 2.9 integrated less than 1 H. [e] Obtained as the monohydrate. [f] Crystallized from water. [g] Satisfactory analytical data (±0.5% for C, N, H) were reported for all compounds in the table.

Table IV. Physical Data for Pyrido[2,3-*d*]pyrimidine Derivatives 9, 10, 12[d]

			^{1}H NMR (Me_2SO-d_6), δ	
compd	mp, °C	UV data,[a] λ_{max}, nm ($10^3\epsilon$)	H-5	other
9a	288-289	313 (11.5),[b] 304 (12.7), 262 (6.7), 213 (28.1)	8.14 d[c]	3.29 s (3 H, NCH_3), 3.26 s (3 H, NCH_3), 12.08 (NH)
9g	>300	340 (14.7),[b] 328 (15.9), 284 (11.9), 230 (27.7),[b] 221 (32.0)	8.87 s	3.87 s (3 H, NCH_3), 3.60 s (3 H, NCH_3)
9h	239-240	362 (12.2), 291 (13.8), 274 (12.6),[b] 244 (17.6),[b] 228 (25.2)	8.69 s	3.49 s (3 H, NCH_3), 3.27 s (3 H, NCH_3)
9n	242-243	353 (9.5), 330 (9.7), 288 (11.6), 228 (24.0)	8.58 s	3.48 s (3 H, NCH_3), 3.26 s (3 H, NCH_3), 2.61 s (3 H, CCH_3)
9o	>330	333 (19.5), 283 (11.5), 226 (30.2)	8.81 s	3.46 s (3 H, NCH_3), 8.07 (NH)
9x	294-295	337 (17.9), 331 (17.8),[b] 285 (13.9), 230 (33.6),[b] 225 (34.2)	8.53 s	4.09 m (4 H, CH_2CH_3), 1.23 m (6 H, CH_2CH_3)
9y	183-184	356 (10.7),[b] 329 (30.5), 289 (14.4), 228 (30.5)	8.56 s	4.06 m (4 H, CH_2CH_3), 2.61 s (3 H, $COCH_3$), 1.19 m (6 H, CH_2CH_3)
9z	264-265	337 (17.4), 330 (17.3),[b] 286 (13.3), 232 (32.3),[b] 226 (33.6)	8.53 s	3.99 m (4 H, NCH_2), 1.66 m (4 H, CCH_2), 0.89 m (6 H, CH_2CH_3)
10	191-193	363 (18.1), 336 (12.3), 267 (6.0), 235 (16.6),[b] 213 (25.0)	8.20 d[d]	3.68 s (3 H, NCH_3), 3.48 s (3 H, NCH_3)
12	221-223	284 (13.5), 230 (30.5), 224 (29.5)[b]	8.47 s	4.07 t (2 H, NCH_2), 11.65 (NH), 12.4 (NH), 0.7-1.9 m (7 H, $CCH_2CH_2CH_3$)

[a] Taken in EtOH for **9o** (H_2O). [b] Shoulder. [c] H-6 at δ 6.50 ($J_{5,6}$ = 8.0 Hz). [d] H-6 at 7.04 (d, $J_{5,6}$ = 8.0 Hz). [d] See footnote *g* of Table III.

cipitates were collected by filtration, triturated with 0.1 N NaOH (20 mL), and filtered, and the filtrate was acidified to pH 2 with concentrated HCl. The precipitate was collected by filtration and crystallized from EtOH to afford analytically pure **9g**: 520 mg (78%); mp 191–193 °C. See Table IV for physical constants.

1-*n*-Butyl-6-cyanopyrido[2,3-*d*]pyrimidine-2,4,7-(1*H*,3*H*,8*H*)-trione (12). A mixture of **1g** (990 mg, 6 mmol) and 6-amino-1-*n*-butyluracil (549 mg, 3 mmol) in ethanolic sodium ethoxide (230 mg of Na in 40 mL of EtOH) was heated at reflux for 1 h, and then the solvent was removed in vacuo. The residue

was triturated with cold water (20 mL) and filtered. The filtrate was acidified with concentrated HCl to pH 2, and the precipitate was collected and crystallized from water to give 370 mg of **11**. See Table IV for physical and analytical data.

Registry No. **1a**, 874-14-6; **1b**, 4401-71-2; **1d**, 3013-92-1; **1e**, 31217-00-2; **1f**, 7033-39-8; **1g**, 36980-91-3; **1h**, 41613-26-7; **1n**, 36980-95-7; **1o**, 38009-11-9; **2a**, 108-13-4; **2i**, 107-95-1; **2j**, 5977-14-0; **2k**, 103-81-1; **2m**, 75993-39-4; **3a**, 35441-11-3; **3b**, 75993-40-7; **3d**, 75993-41-8; **3e**, 75993-42-9; **3f**, 75993-43-0; **3g**, 52600-58-5; **3i**, 18266-78-9; **3j**, 68999-74-6; **3k**, 10211-36-6; **3m**, 75993-44-1; **4**, 49785-67-3; **5**, 71350-47-5; **6a**, 68999-73-5; **6b**, 53422-09-6; **7**, 71350-48-6; **8a**, 6642-31-5; **8p**, 41740-15-2; **8q**, 41862-14-0; **9a**, 57821-20-2; **9g**, 74115-52-9; **9h**, 74115-55-2; **9n**, 74115-56-3; **9o**, 75993-45-2; **9x**, 74115-53-0; **9y**, 75993-46-3; **9z**, 74115-54-1; **10**, 74115-57-4; **11**, 53681-49-5; **12**, 75993-47-4.

Palladium-Catalyzed Alkenylation of Aromatic Heterocycles with Olefins. Synthesis of Functionalized Aromatic Heterocycles[1]

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Aromatic heterocycles such as furan, thiophene, benzofuran, benzothiophene, and *N*-acetylindole undergo facile palladium-assisted alkenylation with various olefins to produce mono- and/or dialkenylated heterocycles in high yield. With furan and thiophene, the reaction is regioselective, giving products substituted at the 2-position of the heterocycles, and is also stereoselective, giving *E* products when the substituent on the olefin is bulky. The reactions of benzofuran and *N*-acetylindole with olefins give cyclization products such as dibenzofuran and carbazole derivatives together with alkenylated products. The mechanistic implications with respect to these alkenylations are discussed.

The reaction with palladium salts has been intensively studied following the discovery of the Wacker process.[2] We have reported a new reaction which combines aromatic compounds and olefins via direct activation of the both olefinic and aromatic C–H bonds by palladium salts, giving aromatic-substituted olefins. This reaction provides a convenient synthetic method for a wide variety of olefins.[3]

Aromatic heterocycles like furan and thiophene are important starting materials for synthesis of various biologically and physiologically active compounds.[4] However, functionalization of these compounds, especially introduction of alkenyl groups to such heterocycles, is difficult and no general method is known for alkenylation. For example, one has to prepare alkenylated heterocycles via multistep procedures involving formylation and subsequent Wittig reactions.[5]

We have developed a new route to alkenylated aromatic heterocycles by the $Pd(OAc)_2$–$Cu(OAc)_2$ catalyst system. Herein we report the palladium-catalyzed one-step mono- and dialkenylations of five-membered aromatic heterocycles such as furan or thiophene[6] and the reactions of benzofuran, benzothiophene, and *N*-acetylindole with olefins like acrylonitrile, methyl acrylate, and styrene to give cyclization products such as dibenzofuran and carbazole derivatives along with alkenylated products.

Table I. Pd-Assisted Alkenylation of Furan and Thiophene with Olefins (CH_2=CHR)

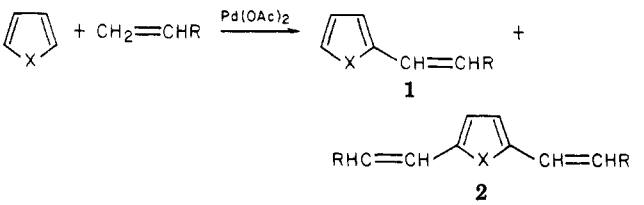
X	R	product, % yield[a] 1	2	stereochemistry
O	CN	23[b]	31[c]	*Z* and *E*
O	Ph	15	46	*E*
O	CO_2CH_3	26	19	*E*
S	CN	24[d]	11[e]	*Z* and *E*
S	Ph	13	36	*E*
S	CO_2CH_3	33	28	*E*

[a] Yields are based on palladium acetate. [b] *Z* and *E* 1:2 mixture. [c] *E,Z* and *E,E* 1:1 mixture. [d] *Z* and *E* 1:2 mixture. [e] *E,Z* and *E,E* 1:1 mixture.

Results and Discussion

Stoichiometric Alkenylation. The alkenylation reactions of furan and thiophene with olefins (CH_2=CHR) were carried out, using equimolar amounts of $Pd(OAc)_2$, the heterocycle, and the olefin in a solution of dioxane and acetic acid. The solution was stirred at 100 °C in the presence of air for usually 8 h. The results are given in Table I.

As can be seen from Table I, furan and thiophene are easily alkenylated with olefins to give 2-alkenylated heterocycles (**1**) and 2,5-dialkenylated heterocycles (**2**) in good



1 **2**

X = O, S
R = CN, Ph, CO_2CH_3

yields. It is interesting that the dialkenylated product is

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