Seven-membered *N*-Heterocycles. XIII.[1] Rearrangement of 7-Benzyl-4-hydroxy-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*d*]azepines to 7-Benzyl-4-vinyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidines

Hiroshi YAMAMOTO, Heizan KAWAMOTO, Shiro MOROSAWA, and Akira YOKOO

Department of Chemistry, Faculty of Science, Okayama University, Tsushima, Okayama 700

(Received July 26, 1976)

The title pyrimidoazepines when treated with phosphoryl chloride underwent rearrangement to the vinylpyrrolo-pyrimidines *via* probable intermediates 5-(2-benzylaminoethyl)-4-chloro-6-vinylpyrimidines. Reduction and subsequent dehydrogenation of the products led to the preparation of 4-ethyl-7*H*-pyrrolo[2,3-*d*]pyrimidines and their 5,6-dihydro derivatives. The structures are discussed on the basis of pK_a values, UV and NMR spectra.

Tetrahydroazepines fused with various heterocycles have been actively synthesized in recent years mainly because of their pharmacological usefulness.[2] We have reported[3] the synthesis of a variety of substituted 4-hydroxy-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*d*]azepines (*e.g.* **1**) by the condensation of *N*-substituted 5-ethoxycarbonyl-1-azacycloheptan-4-ones with various formamidine derivatives. These 4-hydroxypyrimidoazepines have been converted to the versatile 4-chloro derivatives by the usual method[4] (*i.e.* with $POCl_3$ in the presence of $PhNEt_2$ as a catalyst), leading to the preparation of 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*d*]azepines bearing various substituents at the 2,4,7-positions.[3]

On carrying out the above chlorination without catalyst, however, we had noticed a considerable decrease in the yield of the desired 4-chloro compounds along with the simultaneous formation of a certain by-product. We wish to report here the structure of the by-product which was found to form through a rare type of rearrangement, since such a ring transposition of heterocycles has been a topic of current interest.[5]

The present investigation showed that refluxing **1a** in $POCl_3$ (without $PhNEt_2$) for 2—5 h also gave the expected 4-chloro compound[3] **2a** in a reasonable yield (60—70%). The UV spectra of the monocations of **2a** and its dechlorinated derivative[6] **3** did not differ appreciably from those of the neutral species (see Table 1). This implied that the first protonation took place on the azepine ring nitrogen in **2a** and **3** (*cf.* UV spectra and pK_a values of pyrimidine[7,8] and benzylamine[9,10]).

Prolonged heating of **1a** (*e.g.* for 34 h) with $POCl_3$ and subsequent chromatographic separation of the reaction mixture over alumina, however, resulted in formation of **2a** (40%) and a minor amount of intensely blue-fluorescent (under UV light) colorless prisms. The latter compound had the molecular formula $C_{15}H_{15}N_3$ (thus its yield was 30%). The IR spectrum indicated absence of OH, NH, or C=O group but showed characteristic absorptions at 1635, 980, and 930 cm^{-1}, indicative of the presence of a vinyl group. In contrast to **2a** and **3** the by-product had the longest wavelength UV absorption maximum at 324 nm which, on protonation (pK_a 5.94), showed a hypsochromic shift of *ca.* 20 nm with an increased intensity (Table 1); this is reminiscent of the UV spectra of 4-aminopyrimidines (see below). Since 4-vinylpyrimidine has been reported[11] to exhibit a strong, blue fluoresecnce under UV light, the presence of a vinyl group attached to a 4-aminopyrimidine nucleus was thought to account for the intense fluorescence and the UV of the by-product. The NMR spectrum of the by-product markedly differed from that of **2a** (Table 2) in the following respects: 1) a down-field shift (1.0 ppm) of the benzyl methylene singlet (at δ 4.59) of the by-product and 2) splitting of the complex azepine ring methylene absorptions (8H) of **2a** into a quasi-A_2B_2 methylene signal (4H; centered at δ 3.20) and a typical ABX vinyl signal (at δ 6.60, 6.28, and 5.54). The remaining absorptions in the spectrum of the by-product were two singlets at δ 7.27 (5H; Ph) and 8.39 (1H; pyrimidine ring proton); no deuterium-exchangeable proton was present. Combination of these spectral data led to the structure **4a** 7-benzyl-4-vinyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine for the by-product; the assignments of the NMR signals are shown in Table 2.

Heating the 2-methylpyrimido-azepine (**1b**) with $POCl_3$ analogously produced a mixture of the chloro compound[3] (**2b**) and the similar rearranged product (**4b**); yields of **2b** and **4b** (from **1b**) *vs.* reaction time are shown in Table 3. The UV and NMR spectra of **2b** and **4b**, which closely resembled those of **2a** and **4a**, respectively, were consistent with the structures (see Tables 1 and 2). The pK_a of **4b** (6.95) was one unit higher than that of **4a**, while the pK_a difference between **2b** and **2a** was 0.35. This can be explained in terms of the large base-strengthening effect of a methyl group (usually 0.8 unit) when it is α- or γ- to ionizing nitrogen.[12]

The 2-phenyl derivative **1c**, made by the condensation of 1-benzyl-5-ethoxycarbonyl-1-azacycloheptan-4-one with benzamidine, gave only the 4-chloro compound **2c** in good yield when treated with boiling $POCl_3$ for 2—5 h. Heating of **1c** with $POCl_3$ at an elevated temperature (160 °C) in a sealed tube, however, produced the similar rearranged product **4c** in 38% yield; the physical properties of **4c**, recorded in Tables 1 and 2, were in conformity with the structure. The same reaction of the 2-amino compound[3] **1d** with $POCl_3$ yielded a mixture of several intractable products.[13]

The structure **4a** was confirmed by examining the spectra of the hydrogenated derivative **5a** readily obtainable as colorless prisms with the molecular formula of $C_{15}H_{17}N_3$. Its IR and NMR spectra (Table 2) clearly showed the conversion of the vinyl group of **4a** to an ethyl group, indicating the structure 7-benzyl-4-ethyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine for **5a**.

TABLE 1. IONIZATION CONSTANTS AND UV SPECTRA[a]

Compound	Species[c]	Ionization in water (20°C)			Spectroscopy[b] in water		
		pK_a	Concn (M)	A.w.l.[d]	λ_{max}(nm)	log ε	pH
2a	+	6.70±0.05	3.9×10^{-5}	230	*252*, 257, *261*	*3.66*, 3.70, *3.62*	3.8
	0				*253*, 258, *263*	*3.69*, 3.73, *3.66*	8.9
3	++	0.65±0.1	6.7×10^{-5}	254	254	3.75	−1.3
	+	7.05±0.05	6.7×10^{-5}	227	251, *255*, 268	3.60, *3.56*, 2.94	4.9
	0				253, *255*, *273*	3.62, *3.61*, *2.99*	9.8
2b	+	7.05±0.04	2.2×10^{-4}	234	261, *267*,	3.67, *3.56*	1.7
	0				262, *268*	3.67, *3.59*	9.1
2c	+	7.0[e]	3.1×10^{-5}	230	262, *267*, *291*	4.30, *4.28*, *3.73*	3.6
	0				265, *268*, *293*	4.38, *4.37*, *3.84*	EtOH[f]
4a	+	5.94±0.03	7.0×10^{-5}	295	*298*, 305, *315*, *330*, *345*	*4.12*, 4.13. *4.10*, *3.96*, *3.65*	2.9
	0				225, 229, 270, 324, *330*, *349*	4.29, 4.29, 3.90, 3.87, *3.85*, *3.58*	9.0
4b	+	6.95±0.05	4.6×10^{-5}	291	*226*, *235*, 296, 305, *315*, *328*	*4.20*, *4.08*, 4.11, 4.12, *4.10*, *3.97*	2.7
	0				220, *227*, *236*, *249*, 265, 325	4.35, *4.32*, *4.27*, *4.11*, 3.96, 3.94	9.5
4c	+	5.40±0.03[g]	1.9×10^{-5}	238	*245*, 261, 307	*4.23*, 4.31, 4.07	2.0
	0				240, 291, 338	4.55, 3.89, 3.84	EtOH[f]
5a	+	6.68±0.02	6.2×10^{-5}	280	279	4.23	3.8
	0				*261*, 265, *286*	*4.11*, 4.12, *3.78*	9.8
5b	+	7.75±0.02	4.0×10^{-5}	277	277	4.23	1.5
	0				263, *285*	4.08, *3.87*	10.0
5c	+	6.20±0.02[g]	4.5×10^{-6}	261	258, *275*	4.47, *4.35*	2.0
	0				247, 271, 312	4.41, 4.10, 3.73	EtOH[f]
6b	+	5.10±0.02	6.6×10^{-5}	271	226, 271, 297	4.43, 3.52, 3.37	2.0
	0				221, 273, *283*	4.40, 3.66, *3.62*	8.7
	−	13.3 ±0.1[h]	6.6×10^{-5}	280	231, 279, 313	4.35, 3.71, 3.26	15
7-Deaza-purine[i]	+	[j]			225, 265, 299	4.44, 3.49, 3.18	1
	0				271	3.60	6.8
	−	[j]			273	3.59	NaOH
6d	+	5.91±0.03	5.4×10^{-5}	288	227, 274, 303	4.44, 3.52, 3.35	3.0
	0	[k]			222, *270*, 280	4.42, *3.63*, 3.66	9.0
6e	+	4.24±0.01[g]	1.9×10^{-5}	257	255, 303	4.45, 4.04	2.0
	0				257, 302	4.44, 4.12	EtOH[f]
6f	+	4.88±0.04	2.0×10^{-5}	272	250, 298	4.41, 4.10	2.0
	0				250, 291	4.41, 4.05	7.7
	−	13.4 ±0.1[h]	2.0×10^{-5}	270	263, *332*	4.36, *3.65*	15

a) Measured with a Hitachi EPS 3T Recording Spectrophotometer. b) Inflections in italics. c) Dication (++), monocation (+), neutral species (0), monoanion (−). d) Analytical wavelength in nm (*cf.* Ref. 23). e) Approx. value because the neutral species is hardly soluble in water. f) In 95 v/v% ethanol. g) In 0.01 M buffers containing 25 v/v% ethanol because the neutral species is hardly soluble in the buffers alone. h) Approx. i) From Ref. 16. j) No pK_a values have been reported. k) The acidic $pK_a > 14$.

The close resemblance of the UV of **5a** (pK_a 6.68; Table 1) to those of structurally similar 4-dimethylaminopyrimidine (pK_a 6.35)[14] further supported the structure; the longest wavelength absorption maxima of the neutral species of both compounds showed about 7 nm hypsochromic shift (with increased intensities) on protonation. The 2-methyl- and 2-phenyl-4-vinylpyrrolo-pyrimidine **4b** and **4c** were also readily reduced to the 4-ethyl derivatives **5b** and **5c**, respectively. Those spectral properties evidently supported the structures (see Tables 1 and 2 for UV and NMR spectra).

Synthesis of a variety of substituted pyrrolo[2,3-*d*]-pyrimidines ("7-deazapurines") and their 5,6-dihydro derivatives has been drawing an increasing interest in view of their biological importance recently.[15] When our dihydropyrrolopyrimidine **5a** was heated in decalin in the presence of 10% Pd–C, a mixture of 7-benzyl-4-ethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**6a**) and the debenzylated derivative (**6b**) (in 27 and 33% yields, respectively) was produced, the latter (**6b**) being presumably derived from **6a** by reduction with the hydrogen absorbed on the catalyst. The fully aromatic structures for **6a** and **6b** were confirmed by

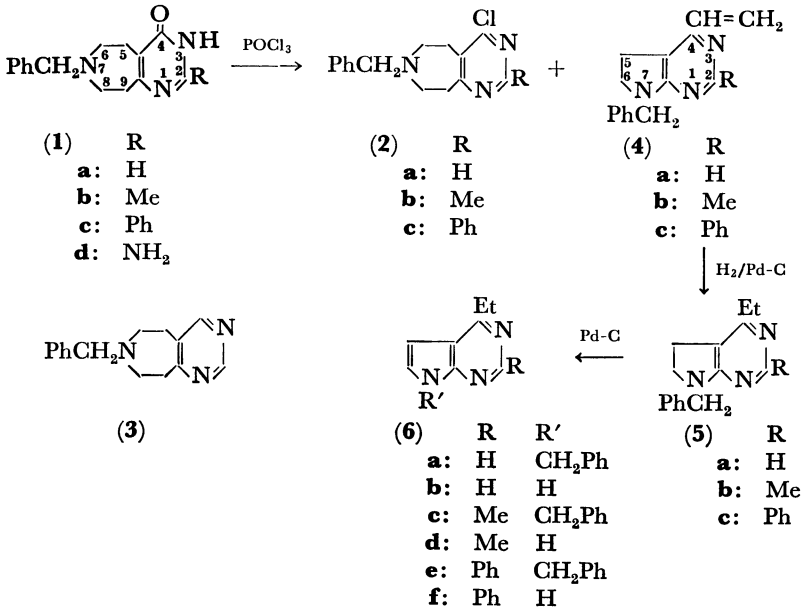
Table 2. ^{1}H-NMR spectra[a]

Compound	δ-Values[b] for H-2	H-4	H_2-5,9	H_2-6,8	H-7
1c	7.25—7.6 m (3H)[c] 8.25 m (2H)[c]	—	2.85—3.20 m	2.05—2.85 m	3.67 s (2H)[d] 7.35 s (5H)[e]
2a[f]	8.59 s	—	2.9 —3.2 m	2.45—2.76 m	3.58 s (2H)[d] 7.25 s (5H)[e]
2b[f]	2.53 s[g]	—	2.85—3.2 m	2.4 —2.75 m	3.56 s (2H)[d] 7.25 s (5H)[e]
2c	7.30—7.56 m (3H)[c] 8.41 m (2H)[c]	—	2.95—3.4 m	2.5 —2.85 m	3.63 s (2H)[d] 7.34 s (5H)[e]
4a	8.39 s	5.54 dd (J=9.1, 3.5)[h] 6.28 dd (J=17.0, 3.5)[i] 6.60 dd (J=17.0, 9.1)[j]	2.8 —3.18 m[k]	3.22—3.7 m[l]	4.59 s (2H)[d] 7.27 s (5H)[e]
4b	2.53 s[g]	5.54 dd (J=10.0, 3.0)[h] 6.27 dd (J=17.0, 3.0)[i] 6.59 dd (J=17.0, 10.0)[j]	2.73—3.13 m[k]	3.25—3.65 m[l]	4.60 s (2H)[d] 7.29 s (5H)[e]
4c	7.30—7.55 m (3H)[c] 8.40—8.65 m (2H)[c]	5.58 dd (J=8.5, 4.5)[h] 6.49 dd (J=16.5, 4.5)[i] 6.70 dd (J=16.5, 8.5)[j]	2.80—3.20 m[k]	3.35—3.75 m[l]	4.72 s (2H)[d] 7.34 s (2H)[e]
5a	8.23 s	1.18 t (J=7.5)[m] 2.42 q (J=7.5)[n]	2.65—3.1 m[k]	3.2 —3.6 m[l]	4.52 s (2H)[d] 7.23 s (5H)[e]
5b	2.38 s[g]	1.18 t (J=7.3)[m] 2.41 q (J=7.3)[n]	2.65—3.1 m[k]	3.2—3.6 m[l]	4.53 s (2H)[d] 7.23 s (5H)[e]
5c	7.30—7.55 m (3H)[c] 8.35—8.55 m (2H)[c]	1.28 t (J=7.5)[m] 2.59 q (J=7.5)[n]	2.75—3.15 m[k]	3.30—3.70 m[l]	4.71 s (2H)[d] 7.34 s (5H)[e]
6a	8.85 s	1.41 t (J=7.5)[m] 3.06 q (J=7.5)[n]	6.58 d[o] J=3.5	7.12 d[p] J=3.5	5.47 s (2H)[d] 7.29 s (5H)[e]
6b	8.88 s	1.44 t (J=7.5)[m] 3.12 q (J=7.5)[n]	6.64 d[o] J=3.5	7.38 bd[q] J=3.5	12.10 m[r]
6c	2.78 s[g]	1.39 t (J=7.5)[m] 3.03 q (J=7.5)[n]	6.50 d[o] J=3.4	6.99 d[p] J=3.4	5.41 s (2H)[d] 7.26 s (5H)[e]
6d	2.85 s[g]	1.40 t (J=7.5)[m] 3.05 q (J=7.5)[n]	6.56 d[o] J=3.4	7.26 bd[q] J=3.4	12.80 m[r]
6e	7.20—7.55 m (3H)[c] 8.45—8.70 m (2H)[c]	1.45 t (J=7.5)[m] 3.04 q (J=7.5)[n]	6.42 d[o] J=3.5	6.94 d[p] J=3.5	5.45 s (2H)[d] 7.23 s (5H)[e]
6f	7.45—7.65 m (3H)[c] 8.35—8.60 m (2H)[c]	1.48 t (J=7.5)[m] 3.15 q (J=7.5)[n]	6.57 dd[o] J=3.5, 1.5	7.14 dd[q] J=3.5, 2.0	12.40 m[r]

a) Measured with a Hitachi High Resolution NMR Spectrometer, R-20A (60 MHz). b) In $CDCl_3$ with TMS as an internal standard, except for compounds **2a**, **2b**, and **6e** (in CCl_4). Suffixes: b, broad; s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; J, coupling constants (Hz). c) For C_6H_5-2. d) For PhCH_2-7. e) For $C_6H_5CH_2$-7. f) Values from Ref. 3 for comparison. g) For Me-2. h, i) For CH_2=CH-4 (*trans* and *cis* with respect to the nucleus, respectively). j) CH_2=C*H*-4. k) For H_2-5. l) For H_2-6. m) For CH_3CH_2-4. n) For CH_3CH_2-4. o) For H-5. p) For H-6. q) For H-6. Becomes doublet on D_2O exchange. r) For H-7; D_2O exchangeable.

the down-field shifts of the coupled doublets (1H each, J=3.5 Hz) due to H-5 and 6 and of the benzyl methylene singlet (in the case of **6a**) in the NMR spectra (see Table 2). The UV spectra of **6b** (Table 1) resembled those of the parent substance[16] (Table 1) and of pyrrolo[2,3-*e*]pyrimidine ("9-deazapurine"),[17] but differed slightly from those of purine[18] by having an extra absorption band in 285—315 nm region. The basic and acidic pK_a values of **6b** were in the similar order to those of 9-deazapurine (pK_a 4.24, 13.16).[17] The 2-methyl compound **5b** also gave a mixture of **6c** and **6d** in 10 and 80% yields, respectively; the physical properties of those products shown in Tables 1 and 2 were similar to those of **6a** and **6b**. The 2-phenyl compound **5c** produced likewise **6e** and **6f** (in 31 and 64% yields, respectively).

A Reaction Pathway for the Formation of the Rearrangement Products ***4***. It was found that the 4-chloro compounds **2a**—**c** also produced mainly **4a**—**c**, when heated with $POCl_3$. The compound **4b** was obtained on heating the monohydrochloride of **2b** at 130 °C in *N*,*N*-dimethylformamide. Thus the rearrangement products **4a**—**c** were most likely formed through the protonated tetrahydropyrimido-azepines **7**, which afforded the ring-opened intermediate 5-(2-benzylaminoethyl)-4-chloro-6-vinylpyrimidines (**8**) through



(1) R: **a**: H, **b**: Me, **c**: Ph, **d**: NH_2

(2) R: **a**: H, **b**: Me, **c**: Ph

(4) R: **a**: H, **b**: Me, **c**: Ph

(3)

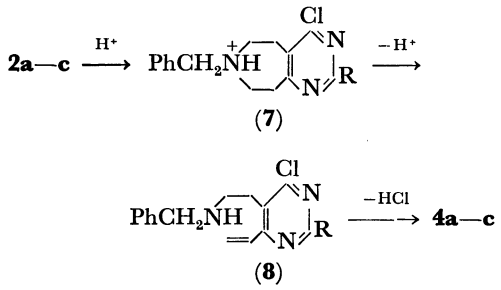
(6) R R′: **a**: H CH_2Ph, **b**: H H, **c**: Me CH_2Ph, **d**: Me H, **e**: Ph CH_2Ph, **f**: Ph H

(5) R: **a**: H, **b**: Me, **c**: Ph

Scheme 1.

TABLE 3. ISOLATED YIELDS OF **2b** AND **4b** FROM **1b**

Chlorinating agents	React. time (h)	**2b** (%)	**4b** (%)
$POCl_3+PhNEt_2$	2	70	10
$POCl_3$	5	50	20
$POCl_3$	8	25	40
$POCl_3$	13	0	45



(7)

(8)

Scheme 2.

Hofmann-type degradation[19] (or retrograde Michael reaction[20]). This ring-opening would preferably take place at the N(7)–C(8) [not N(7)–C(6)] bond of **7**, because the C(9) methylene group (which is α- and γ- to the pyrimidine ring nitrogens) is expected to be more acidic than that of C(5).[21] The intermediate **8** would then yield the final products **4a—c** by the intramolecular cyclization between the 5-(2-benzylaminoethyl) and 4-chloro groups of the pyrimidine ring (Scheme 2). 4-Vinylpyrimidines have been reported[11] to polymerize easily. The main reason for the moderate yields thus far of the rearranged products **4a—c** appeared to be likewise a facile addition polymerization of the vinyl functional group of the products (or of the intermediate **8**), since a considerable amount of a colorless rubberlike substance always accompanied during the preparation and purification of **4a—c**.

Many rearrangements have been known[5] involving fission of a heterocyclic ring and ring closure in the alternative direction catalyzed by base, heat, light or miscellaneous reagents. The present rearrangement seems, to our knowledge, to be a rare example of acid-catalyzed thermal ring transposition of fused heterocycles.[22]

Experimental

The microanalyses were carried out in this department using a Yanagimoto CHN Corder, MT-2. The solid materials for the analysis were dried over P_2O_5 for 2—4 h at 25 °C/20 Torr unless otherwise specified. Each of the analytical samples gave a single spot on thin-layer chromatography (silica gel and alumina). The IR spectra were taken with a JASCO IRA-1 Diffraction Grating IR Spectrophotometer. The measurements of ionization constants were carried out spectrophotometrically in 0.01 M buffers by the usual method.[23]

The Reaction of ***1a*** *with Phosphoryl Chloride.* A mixture of 1.0 g of **1a** and 15 ml of $POCl_3$ was refluxed under N_2 for 34 h. After evaporation of the $POCl_3$ at 40 °C/15 Torr, the residue was triturated with 20 ml of cold water, then diluted with 20 ml of cold chloroform. The aqueous layer was carefully brought to pH 8 with Na_2CO_3 at 5 °C. After separation, the aq. layer was extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over K_2CO_3, and evaporated *in vacuo*, giving 1.14 g of a brown viscous liquid, which consisted mainly of **2a** and **4a** (in a ratio of 3 : 2 by NMR; the ratio was 9 : 1 after 9 hours' refluxing). This was chromatographed over alumina (Merck, Activity I; 60 g) and eluted with benzene (which was gradually changed up to 20% ether/benzene), giving first 0.48 g (40%) of **2a** as colorless prisms (from benzene/light petroleum, bp 30—70 °C), mp 65—67 °C (lit,[3] 67—68 °C), then 0.28 g (30%) of **4a** as colorless prisms (from ether/light petroleum), mp 71—73 °C. IR ($CHCl_3$): 1635, 1592, 1582, 1320, 980, 930, and 855 cm^{-1}. Found: C, 76.02; H, 6.50; N, 17.53%. Calcd for $C_{15}H_{15}N_3$: C, 75.91; H, 6.37; N, 17.71%.

7-Benzyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine ***(3)***. A suspension of 100 mg of **2a** and 100 mg of sodium acetate in 5 ml of abs. EtOH was hydrogenated over 30 mg of 10%

Pd-C under atmospheric pressure, followed by the usual work-up procedure, giving 65 mg (74%) of **3** as colorless prisms (from light petroleum), mp 65—66 °C (lit,[3] 66.5—67.5 °C).

*The Reaction of **1b** with Phosphoryl Chloride.* One gram of **1b** was refluxed in 15 ml of $POCl_3$ and the same procedure as that described for **1a** was followed; the reaction time and the isolated yields of the products are shown in Table 3. The chloropyrimidoazepine (**2b**) was a colorless liquid (bp 170 °C/0.7 Torr[3]), which gave the monohydrochloride with HCl/ether as colorless flakes (from EtOH), mp 204—205 °C dec. Found (for material dried at 80 °C): C, 59.18; H, 6.09; N, 12.97%. Calcd for $C_{16}H_{18}N_3Cl \cdot HCl$: C, 59.28; H, 5.91; N, 12.96%.

The pyrrolo-pyrimidine **4b** was colorless needles (from benzene/light petroleum), mp 96—97 °C. IR ($CHCl_3$): 1635, 1590, 1390, 1340, 980, and 930 cm^{-1}. Found: C, 76.58; H, 6.92; N, 16.30%. Calcd for $C_{16}H_{17}N_3$: C, 76.45; H, 6.82; N, 16.72%.

*The Reaction of **2b** Hydrochloride with Phosphoryl Chloride.* A suspension of 100 mg of **2b** hydrochloride in 2 ml of $POCl_3$ was refluxed under N_2 for 12 h, followed by the same procedure as above, giving 80 mg of the crude reaction mixture as an amber liquid, which consisted mainly of unreacted **2b** and the rearranged **4b** in a ratio of 8 : 2 (by NMR).

*Heating of **2b** Hydrochloride in* N,N-*Dimethylformamide.* A solution of 0.32 g of **2b** hydrochloride in 10 ml of dry DMF was heated under N_2 at 130 °C for 5 h. The volatile was removed at 80 °C/15 Torr and the residue was dissolved in a cold mixture of $CHCl_3$ and 5% aq $NaHCO_3$ (10 : 10 ml). After separation, the aq layer was extracted with $CHCl_3$. The combined organic layer was dried over K_2CO_3 and evaporated *in vacuo*, giving a pale amber liquid (0.48 g). This was chromatographed over silica gel (40 g) into 15 ml fractions with $CHCl_3$ (which was gradually changed up to 2% MeOH/$CHCl_3$) as an eluent. The fractions 8—22 gave 0.10 g (43%) of a colorless solid which consisted mostly of **4b** (by NMR). Recrystallization from benzene/light petroleum afforded pure **4b** as colorless prisms, mp 94—95 °C.

*7-Benzyl-4-hydroxy-2-phenyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*d*]azepine (**1c**).* To a cold solution of 1.15 g of sodium in 60 ml of dry MeOH were added 3.12 g of 1-benzyl-5-ethoxycarbonyl-1-azacycloheptan-4-one hydrochloride[24] and 2.62 g of benzamidine hydrochloride (monohydrate). The mixture was refluxed under N_2 for 4.5 h. After evaporation of the solvent *in vacuo*, the residue triturated with 80 ml of cold water was carefully taken to pH 6 with cold 6M-HCl and stirred at 25 °C for 1 h. The precipitate was collected and recrystallized from 80% EtOH, giving 2.50 g (75%) of **1c** as pale yellow needles, mp 197—199 °C. IR ($CHCl_3$): 3400—3000, 1630, 1600, and 1500 cm^{-1}. Found (for material dried at 80 °C): C, 75.41; H, 6.57; N, 12.62%. Calcd for $C_{21}H_{21}N_3O$: C, 75.10; H, 6.39; N, 12.68%.

*7-Benzyl-4-chloro-2-phenyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*d*]azepine (**2c**).* A mixture of 0.42 g of **1c** and 15 ml of $POCl_3$ was refluxed under N_2 for 5 h. The volatile was removed *in vacuo* and the residue was triturated in 50 ml of cold water. The mixture was taken to pH 9 with Na_2CO_3 at 5 °C and extracted with benzene. The dried (over K_2CO_3) extract was evaporated *in vacuo*, giving 0.37 g (81%) of **2c** as colorless prisms, mp 117—119 °C, after recrystallization from benzene/light petroleum. IR ($CHCl_3$): 1560, 1520, and 1359 cm.$^{-1}$ Found: C, 72.33; H, 6.06; N, 12.03%. Calcd for $C_{21}H_{20}N_3Cl$: C, 72.08; H, 5.76; N, 12.06%.

*7-Benzyl-2-phenyl-4-vinyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (**4c**).* A suspension of 0.33 g of **1c** in 20 ml of $POCl_3$ was heated in a sealed tube at 160—170 °C for 13 h. The same procedure described above for **4a** and **4b** was followed, giving the crude reaction mixture which contained mostly **4c** and a trace of **2c**. Chromatographic purification over alumina (25 g) with $CHCl_3$ as an eluent gave 0.12 g (38%) of **4c** as pale yellow prisms (from benzene/light petroleum), mp 145—146 °C. IR ($CHCl_3$): 1635, 1580, 1560, 1370, 1350, 1320, 980, 930, and 880 cm^{-1}. Found: C, 80.56; H, 6.23; N, 13.16%. Calcd for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41%.

*7-Benzyl-4-ethyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (**5a**).* The vinyl compound **4a** (60 mg) was hydrogenated in 4 ml of abs. EtOH over 30 mg of 10% Pd-C. The usual work-up procedure yielded 49 mg (81%) of **5a** as colorless prisms (from light petroleum), mp 41—42 °C. Found: C, 75.42; H, 7.20; N, 17.31%. Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56%.

*7-Benzyl-4-ethyl-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (**5b**).* The vinyl compound **4b** (100 mg) was similarly hydrogenated, giving 81 mg (80%) of **5b** as colorless prisms (from light petroleum), mp 72—73 °C. Found: C, 75.46; H, 7.67; N, 16.10%. Calcd for $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.59%. The picrate: yellow prisms (from EtOH), mp 138—139 °C. Found: C, 54.65; H, 4.54; N, 16.81%. Calcd for $C_{22}H_{22}N_6O_7$: C, 54.77; H, 4.60; N, 17.42%.

*7-Benzyl-4-ethyl-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (**5c**).* The similar hydrogenation of 100 mg of **4c** gave 85 mg (85%) of **5c** as colorless needles (from ether/light petroleum), mp 89—90 °C. Found: C, 79.69; H, 6.84; N, 13.07%. Calcd for $C_{21}H_{21}N_3$: C, 79.96; H, 6.72; N, 13.32%.

*Dehydrogenation of **5a**.* A mixture of 60 mg of **5a** and 30 mg of 10% Pd-C was refluxed in 1 ml of dry decalin under N_2 for 17 h. The catalyst was filtered off and washed with hot benzene. The filtrate combined with washings was concentrated at 20 °C/15 Torr to *ca.* 1 ml and set aside at 0 °C overnight, depositing 8 mg of *4-ethylpyrrolo[2,3-*d*]-pyrimidine (**6b**).* The filtrate was chromatographed over silica gel (5.5 g) and eluted with benzene, then with $CHCl_3$ (which was gradually changed up to 2% MeOH/$CHCl_3$), giving first 17 mg (27%) of *7-benzyl-4-ethylpyrrolo-[2,3-*d*]pyrimidine (**6a**)* as a colorless liquid, then 5 mg of more **6b** as a colorless crystalline powder. Recrystallization of the latter (**6b**; 33% total yield) from benzene/light petroleum gave colorless needles, mp 99—100 °C. IR ($CHCl_3$): 3430, 3200, 3150, 1580, 1345, and 890 cm^{-1}. Found: C, 65.53; H, 6.44; N, 28.55%. Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55%. The benzyl compound **6a** gave the picrate as yellow prisms (from EtOH), mp 153—154 °C. Found: C, 54.28; H, 3.92; N, 18.31%. Calcd for $C_{21}H_{18}N_6O_7$: C, 54.08; H, 3.89; N, 18.02%.

*Dehydrogenation of **5b**.* A mixture of 70 mg of **5b**, 40 mg of 10% Pd-C, and 1.2 ml of dry decalin was refluxed under N_2 for 10 h. The similar work-up procedure as above was followed, giving 36 mg (80%) of *4-ethyl-2-methylpyrrolo-[2,3-*d*]pyrimidine (**6d**)* and 7 mg (10%) of the 7-benzyl derivative (**6c**). The latter was a colorless liquid. IR ($CHCl_3$): 2910, 2840, 1580, 1440, and 1400 cm^{-1}. It gave the picrate as yellow prisms (from EtOH), mp 137—138 °C. Found: C, 55.33; H, 4.20; N, 17.63%. Calcd for $C_{22}H_{20}N_6O_7$: C, 55.00; H, 4.20; N, 17.49%.

The former (**6d**) was colorless needles (from benzene/light petroleum), mp 141—142 °C. IR ($CHCl_3$): 3460, 3120, 1580, 1390, and 885 cm^{-1}. Found: C, 67.30; H, 7.22; N, 26.32%. Calcd for $C_9H_{11}N_3$: C, 67.05; H, 6.88; N, 26.07%.

*Dehydrogenation of **5c**.* Fifty milligrams of **5c** upon

similar dehydrogenation gave 15 mg (64%) of *4-ethyl-2-phenylpyrrolo[2,3-d]pyrimidine (**6f**)* and 10 mg (31%) of the 7-benzyl derivative (**6e**). The latter (**6e**) was colorless needles (from light petroleum), mp 46—47 °C. IR ($CHCl_3$): 1600, 1575, 1560, 1390, and 1370 cm^{-1}. Found: C, 80.11; H, 6.24; N, 13.17%. Calcd for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41%. The former (**6f**) was colorless needles (from ether/light petroleum), mp 139—140 °C. IR ($CHCl_3$): 3480, 3200, 3140, 1580, 1380, 900, 800, and 690 cm^{-1}. Found: C, 74.91; H, 5.96; N, 18.49%. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82%.

References

1) Part XII. H. Kawamoto, T. Matsuo, S. Morosawa, and A. Yokoo, *Bull. Chem. Soc. Jpn.*, **46**, 3898 (1973).

2) *e.g.* See a) J. B. Hester, Jr., Fr. M. 6699; *Chem. Abstr.*, **75**, 5876 (1971) for 6-alkyl-1,2,3,4,5,6-hexahydroazepino-[4,5-*b*]indoles; b) G. Griss, M. Kleemann, W. Grell, and H. Ballhause, Ger. Offen. 2127267; *Chem. Abstr.*, **79**, 78777 (1973) for 2-amino-4,5,7,8-tetrahydro-6*H*-oxazolo[5,4-*d*]azepines.

3) H. Yamamoto, M. Nakata, S. Morosawa, and A. Yokoo, *Bull. Chem. Soc. Jpn.*, **44**, 153 (1971).

4) *e.g.* See D. J. Brown, "The Pyrimidines," Interscience, New York (1962), p. 162.

5) H. C. van der Plas, "Ring Transformation of Heterocycles," Academic Press, New York (1973).

6) Compound **3**, which has been made from **2a** *via* the 4-hydrazino derivative and subsequent oxidation with Ag_2O (Ref. 3), is now readily available by simple catalytic hydrogenation, see Experimental.

7) a) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, **1951**, 474; b) M. P. Boarland and J. F. W. McOmie, *ibid.*, **1952**, 3716. λ_{max} (pH 0) 242 nm (log ε 3.6) λ_{max} (pH 7) 243, 272 nm (log ε 3.4, 2.5).

8) A. Albert, R. J. Goldaere, and J. Phillips, *J. Chem. Soc.*, **1948**, 2240: pK_a 1.30.

9) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," Wiley, New York (1951).

10) E. J. Robinson and A. K. Kiang, *Trans. Faraday Soc.* **52**, 327 (1956): pK_a 9.35.

11) C. G. Overberger and I. C. Kogon, *J. Am. Chem. Soc.*, **76**, 1879 (1954).

12) A. Albert, "Heterocyclic Chemistry," 2nd ed, Athlone Press, London (1968), p. 437.

13) Conversion of hydroxy groups of pyrimidines into chloro groups in the presence of amino groups frequently encounters difficulties, see Ref. 4.

14) D. J. Brown and L. N. Short, *J. Chem. Soc.*, **1953**, 331: λ_{max} (pH 3.15) 262 nm (log ε 4.31), λ_{max} (pH 9.3) 250, 286 nm (log ε 4.22, 3.56).

15) a) For a review, see V. Amarnath and R. Madhav, *Synthesis*, **1974**, 837; b) H. Wolfers, U. Kraatz, and F. Korte, *Heterocycles*, **3**, 187 (1975); c) H. J. Roth and K. Eger, *Arch. Pharm. (Weinheim, Ger.)*, **308**, 252 (1975); *Chem. Abstr.*, **83**, 97187 (1975); d) D. H. Kim and A. A. Santilli, U. S. 3910913; *Chem. Abstr.*, **84**, 31116 (1976); e) A. A. Santilli, A. C. Scotese, and D. H. Kim, *J. Heterocyclic Chem.*, **13**, 135 (1976).

16) a) Wellcome Foundation Ltd., Brit. 812366; *Chem. Abstr.*, **54**, 592 (1960); b) J. Davoll, *J. Chem. Soc.*, **1960**, 131.

17) A. Albert, *Chem. Ind.*, **1970**, 365.

18) a) S. F. Mason, *J. Chem. Soc.*, **1954**, 2071; b) A. Albert and C. Pendersen, *ibid.*, **1956**, 4683.

19) *e. g.* For a review, see A. C. Cope and E. R. Trumbell, *Org. React.*, **11**, 320 (1960).

20) *e.g.* See H. O. House, "Modern Synthetic Reactions," 2nd ed., Benjamin, 1972, pp. 595—623 and references cited therein.

21) 4-Methyl group of pyrimidines is generally more acidic than 5-methyl group; see W. Pfleiderer and H. Mosthaf, *Chem. Ber.*, **90**, 728 (1957).

22) Applications of this reaction to synthesis of other heterocycles are currently under investigation.

23) A. Albert and E. P. Serjeant, "Ionization Constants of Acid and Base," Methuen, London (1962).

24) T. Moriya, T. Oki, S. Yamaguchi, S. Morosawa, and A. Yokoo, *Bull. Chem. Soc. Jpn.*, **41**, 230 (1968).