Studies of Seven-Membered Heterocyclic Compounds Containing Nitrogen. X. Syntheses of 5,6,8,9-Tetrahydro-7*H*-pyrimido[4,5-*d*]azepines

Hiroshi YAMAMOTO, Masaru NAKATA,[1] Shiro MOROSAWA, and Akira YOKOO

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

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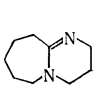
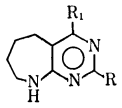
5,6,8,9-Tetrahydro-7*H*-pyrimido[4,5-*d*]azepine and some of its derivatives were synthesized. 6-Acetyl-3-hydroxy-4,5,7,8-tetrahydro-6*H*-pyrazolo[3,4-*d*]azepine was also synthesized.

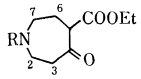
The previously-known compounds which have pyrimido-azepine ring systems are 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine (I)[2] and 5,6,7,8-tetrahydro-9*H*-pyrimido[4,5-*b*]azepines (II).[3] As an extensive investigation of *N*-substituted 5-ethoxycarbonyl-1-azacycloheptan-4-one, which has been prepared from the corresponding *N*-substituted piperid-4-ones by ring expansion with ethyl diazoacetate,[4] and especially in order to obtain azepine compounds by the dehydrogenation of the corresponding hydroazepines, the syntheses of the tetrahydroazepines fused with the pyrimidine ring were undertaken.



I

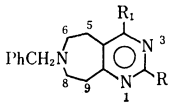


II



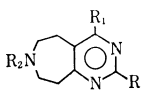
III

a : R=CH_2Ph
b . R=Ac



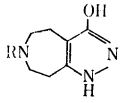
IV

a: R=SH, R_1=OH
b: R=Me, R_1=OH
c: R=NH_2, R_1=OH
d: R=NHCN, R_1=OH
e: R=NHAc, R_1=OH
f: R=H, R_1=OH
g: R=H, R_1=Cl
h: R=H, R_1=OMe
i: R=H, R_1=NH_2
j: R=H, R_1=$NHNH_2$
k: R=H, R_1=H
l: R=Me, R_1=Cl
m: R=Me, R_1=$NHNH_2$
n: R=Me, R_1=H



V

a: R=H, R_1=H, R_2=H
b: R=SH, R_1=OH, R_2=Ac
c: R=Me, R_1=OH, R_2=Ac
d: R=H, R_1=OH, R_2=Ac
e: R=H, R_1=OH, R_2=H
f: R=H, R_1=SH, R_2=CSMe



a: R=Ac
b: R=CH_2Ph

Upon the treatment of the *N*-benzyl-5-ethoxycarbonyl-1-azacycloheptan-4-one (IIIa) with thiourea, acetamidine, guanidine, and cyanoguanidine in the usual way, 2-mercapto-, 2-methyl-, 2-amino-, and 2-cyanamino-7-benzyl-4-hydroxy-5,6,8,9-tetrahydro-7*H*-pyrimido[4,5-*d*]azepines (IVa, b, c and d) were obtained. The structures of these compounds were derived by a study of the analytical and the spectral data. They all showed broad bands at 3100—2800 (medium) and 1665—1645 (strong) cm^{-1}, assignable to the amido group, indicating that the pyrimidine ring existed as a 3,4-dihydro-4-oxo form in solid states. The amino-pyrimido-azepine (IVc), when heated with acetic anhydride, readily gave a 2-acetamido derivative (IVe). The reduction of the mercapto compound (IVa) over Raney nickel yielded the hydroxypyrimido-azepine (IVf), and the IR spectrum indicated the presence of the 3,4-dihydro-4-oxo-pyrimidine structure (ν_{max} 2800 and 1660 cm^{-1}). The hydroxyl group of IVf could be replaced by a chlorine atom with phosphoryl chloride in the presence of diethylaniline, giving the chloro-pyrimido-azepine (IVg). The structure of this compound was confirmed by the IR (no absorption due to an amido group) and the NMR spectra. The assignment of the NMR signals is shown in the Table 1. On taking into account the chemical shift (τ 7.35) of the methylene protons at the 2 and 7 positions (*i. e.*, adjacent to the *N*-benzyl group) of 1-benzyl-1,4-diazacycloheptan-5-one,[5] the multiplet at τ 7.25—7.55 was assigned to the four protons at the 6 and 8 positions; thus, the multiplet at τ 6.80—7.10 was considered to be due to the methylene groups at the 5 and 9 positions.

Various nucleophilic substitution reactions took place on the IVg compound under conditions similar to those on 4,5-dialkyl-6-chloropyrimidines. Upon treatment with sodium methoxide in boiling methanol, ethanolic ammonia at 130°C, and hydrazine hydrate in boiling ethanol, 4-methoxy-, 4-amino-, and 4-hydrazino-pyrimido-azepine (IVh, i, and j respectively) were obtained. IVj gave 7-benzyl-5,6,8,9-tetrahydro-7*H*-pyrimido[4,5-*d*]azepine (IVk) on oxidation with silver oxide in methanol. The NMR spectrum of IVk was in conformity with the structure shown in Table 1. The assignment of the singlets at τ 1.20 and 1.74 to the protons at the 2 and 4 positions respectively was made on the grounds of the H(4) signal (τ 1.87) of the 2-methylpyrimido-azepine (IVn). A slight up-field shift of the signal of H(5) compared with that of IVg is

1) Present address: Nihon Kayaku Co., 1-6 Marunouchi, Chiyoda-ku, Tokyo.

2) a) H. Oediger and Fr. Moller, *Angew. Chem., Int. Ed. Engl.*, **6**, 76 (1967). b) Farbenfabriken Bayer A.-G., Fr. 1491791; *Chem. Abstr.*, **69**, 67412 (1968).

3) a) V. G. Granik and R. G. Glushkov, *Khim. -Farm. Zh.*, **1**, 21 (1967). b) K. Morita, S. Kobayashi, H. Shimadzu, and M. Ochiai, *Tetrahedron Lett.*, **1970**, 861.

4) T. Moriya, T. Oki, S. Yamaguchi, S. Morosawa, and A. Yokoo, This Bulletin, **41**, 230 (1968).

5) M. Sakakida, A. S. Kumanireng, H. Kawamoto, and A. Yokoo, to be published in This Bulletin.

TABLE 1. ASSIGNMENT OF NMR SIGNALS[a)]

Compound	τ Values[b)] for					
	H (2)	H (4)	H_2 (5)[c)]	H_2 (6, 8)[c)]	H_2 (9)[c)]	Substituent
IVg	1.41 s	—	6.80—7.10 m	7.25—7.55 m	6.80—7.10 m	2.75 s (C_6H_5) 6.42 s ($PhCH_2$)
IVk	1.20 s	1.74 s	7.10—7.60 m	7.10—7.60 m	6.80—7.10 m	2.73 s (C_6H_5) 6.39 s ($PhCH_2$)
IVn	—	1.87 s	7.10—7.60 m	7.10—7.60 m	6.80—7.10 m	2.75 s (C_6H_5) 6.40 s ($PhCH_2$) 7.46 s (CH_3)
Ve	1.98 s	—	6.55—7.30 m	6.55—7.30 m	6.55—7.30 m	—

a) Measured by a Hitachi High Resolution NMR Spectrometer, R-20A.
b) In CCl_4 with TMS as an internal standard, except for compound Ve (in D_2O). Suffixes: s, singlet; m, multiplet.
c) Too complicated to determine the accurate chemical shifts.

probably attributable to the removal of the influence of the chlorine atom at the 4 position. The catalytic debenzylation of IVk over 10% palladium on carbon yielded 5,6,8,9-tetrahydro-7*H*-pyrimido[4,5-*d*]azepine (Va) as a colorless oil.

The action of phosphoryl chloride on IVb similarly gave the chloropyrimido-azepine (IVl), but the product appeared to decompose appreciably on distillation. Therefore, the crude product, without purification, was treated with hydrazine hydrate, giving the hydrazinopyrimido-azepine (IVm) in a 67% yield (overall from IVb). IVm was converted into 7-benzyl-2-methyl-5,6,8,9-tetrahydro-7*H*-pyrimido[4,5-*d*]azepine (IVn) by oxidation with silver oxide. The structure was confirmed by the NMR spectrum, the assignment of which is given in Table 1. The catalytic debenzylation of IVn was attempted as in IVk, but the product expected to be similar to Va was not obtained. This is probably due to some decomposition of the starting material during the reaction.

1-Acetyl-1-azacycloheptan-4-one (IIIb) was prepared, by the ring expansion of 1-acetylpiperid-4-one with ethyl diazoacetate, in a relatively good yield (55—65%) compared with that of the same reaction[4)] of 1-benzyl- or 1-ethoxycarbonylpiperid-4-one. The IR spectrum of IIIb showed three strong bands, at 1735, 1715, and 1660 cm^{-1}, assignable to the ethoxycarbonyl, the ring carbonyl, and the acetyl groups respectively. Upon treatment with thiourea and acetamidine, IIIb afforded 2-mercapto- and 2-methyl-7-acetyl-4-hydroxy-5,6,8,9-tetrahydro-7*H*-pyrimido[4,5-*d*]azepine (Vb and c) respectively. The presence of a secondary amido absorption in the IR spectra showed that these compounds exist as the 4-oxo form. Vb was reduced to give the 7-acetyl-4-hydroxypyrimido-azepine (Vd). On refluxing with 6N hydrochloric acid, Vd yielded the hydrochloride of hydroxypyrimido-azepine (Ve) as colorless prisms. The NMR spectrum of the hygroscopic free base in heavy water showed a singlet (1H) at τ 1.98 due to the aromatic ring proton and a complicated multiplet (8H) at 6.55—7.30 due to the tetrahydroazepine ring protons. An attempt to replace the hydroxyl group of Vd with a chlorine atom under conditions similar to those used for the *N*-benzyl compounds (IVb and f) gave only a black, intractable tar. It was found, however, that phosphorus pentasulfide affected both the hydroxyl and acetyl groups of Vd, giving the 4-mercapto-7-thioacetylpyrimido-azepine (Vf). The IR spectrum showed no amido absorption.

6-Acetyl-3-hydroxy-4,5,7,8-tetrahydro-6*H*-pyrazolo-[3,4-*d*]azepine (VIa) was derived from IIIb and hydrazine hydrate as in the case of the benzyl derivative (VIb).[4)]

Experimental

The microanalyses were carried out by Miss H. Ohtani in this department, using a Yanagimoto C.H.N. Corder, MT-1. The solid materials for the analysis were dried over phosphorus pentoxide for 1—2 hr at 80°C/20 mmHg unless otherwise specified. Each of the analytical samples gave a single spot on a paper chromatogram (Toyo Roshi, No. 51) which was developed with 3% aqueous ammonium chloride or 5N acetic acid/1-butanol (29 : 71 v/v) and which was examined under ultraviolet light at 365 and 254 mμ alternately. The IR spectra were taken with a Nihon-Bunko IR-S spectrophotometer; the relatively intense absorption bands of each compound are shown by suffixes (s, strong; br, broad).

*4-Hydroxy-2-mercapto-5, 6, 8, 9-tetrahydro-7*H*-pyrimido*[*4, 5*-d]*-azepine (IVa).* Fifteen grams of IIIa hydrochloride[4)] were shaken with 100 m*l* of 10% aqueous potassium carbonate, and the mixture was extracted with ether. After the ether solution had been dried over anhydrous potassium carbonate and the solvent had been completely removed *in vacuo*, the residual oil was dissolved in 50 m*l* of absolute ethanol; a cold solution of 1.75 g (1.5 equiv) of sodium in 150 m*l* of absolute ethanol was then added. Four grams (1.25 equiv) of thiourea were then added, and the whole was refluxed for 7 hr with stirring. The solvent was evaporated *in vacuo*, and the viscous residue was stirred at 0°C with 50 m*l* of water until it became a powder (*ca.* 6 hr). It was collected, dried in a vacuum desiccator with calcium chloride, and boiled with 200 m*l* of methanol. After having been cooled, the precipitate was collected by filtration to give 6.65 g of IVa as an almost colorless powder; mp 232—236°C. On the concentration of the filtrate to *ca.* 30 m*l*, 0.4 g more of the material was obtained (total yield, 51%). Recrystallization from 50% aqueous ethanol gave almost colorless leaflets; mp 236—238°C. The material is moderately soluble in ethanol, and soluble with difficulty in cold water, 10% aqueous sodium carbonate, and N sodium hydroxide, and it gives a hydrochloride as a colorless powder in N hydrochloric acid.

Found: C, 62.83; H, 6.14; N, 14.43%. Calcd for $C_{15}H_{17}N_3OS$: C, 62.69; H, 5.96; N, 14.62%. ν_{max}^{KBr} 3060 br, 2920 br,

1645 sbr, 1590 sbr, 1560 s, 1230 s, 1215, 1118, 950, 910 br, 735 s, and 695 s cm^{-1}.

*7-Benzyl-4-hydroxy-2-methyl-5,6,8,9-tetrahydro-7*H*-pyrimido[4,5-d]azepine (IVb).* To a solution of 1.2 g (5 equiv) of sodium in 50 m*l* of absolute ethanol were added 3.1 g of IIIa hydrochloride and 1.4 g (1.5 equiv) of acetamidine hydrochloride; the mixture was then heated under reflux for 4 hr. The precipitate was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. Ten milliliters of water were added to the residue, and the resulting solution was washed with ether; then the aqueous layer was brought to pH 5 by the addition of acetic acid. The precipitate which appeared was collected by filtration, washed with a small amount of cold water, and recrystallized from ethanol, thus giving 1.8 g (67%) of IVb as colorless needles; mp 206—208°C. One more recrystallization from ethanol gave an analytical specimen; mp 211—212°C. The material is easily soluble in acetone, and moderately so in chloroform.

Found: C, 71.03; H, 7.08; N, 15.50%. Calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60%. ν_{max}^{KBr} 2800 br, 1656 sbr, 1610 s, 1570, 1435, 1352, 1343, 1308, 1222, 1159, 981, 959 s, 809, 751 s, 736, and 700 cm^{-1}.

*2-Amino-7-benzyl-4-hydroxy-5,6,8,9-tetrahydro-7*H*-pyrimido[4,5-d]azepine (IVc).* A mixture of 5.0 g of IIIa hydrochloride, 5.0 g (3.3 equiv) of guanidine hydrochloride, and 1.2 g (3.3 equiv) of sodium in 100 m*l* of absolute methanol was treated such as in the preparation of IVb. After recrystallization from methanol, 2.7 g (63%) of IVc were obtained as a colorless crystalline powder; mp 252—254°C. The material is soluble in water only with difficulty.

Found: C, 62.94; H, 7.34; N, 18.31%. Calcd for $C_{15}H_{18}N_4O\cdot CH_3OH$: C, 63.55; H, 7.33; N, 18.53%. The methanol of crystallization was not removed on drying even at 110°C. ν_{max}^{KBr} 3360 br, 3050 br, 2890 br, 1650 sbr, 1600 sbr, 1497, 1380, 1369, 1309, 1230, 1190, 1029 br, 948, 793, 779, 750 s, and 693 cm^{-1}.

*7-Benzyl-2-cyanamino-4-hydroxy-5,6,8,9-tetrahydro-7*H*-pyrimido-[4,5-d]azepine (IVd).* From 3.1 g of IIIa hydrochloride, 0.84 g (1.0 equiv) of cyanoguanidine, and 2.0 g (3.7 equiv) of sodium methoxide dissolved in 50 m*l* of absolute methanol, IVd was obtained according to the same precedures as those used for IVb. Two recrystallizations from methanol gave 0.7 g (24%) of IVd as a colorless crystalline powder; mp 254—256°C. The analytical specimen was dried at 25°C/20 mmHg.

Found: C, 65.61; H, 6.02; N, 23.78%. Calcd for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71%. ν_{max}^{KBr} 2950 sbr, 2800 sbr, 2205 s, 1675 sbr, 1640 sbr, 1545, 1497, 1450, 1440, 1380, 1370, 1308, 1268, 1179, 1117, 948, 782, 770, 748, 733 s and 694 cm^{-1}.

*2-Acetamido-7-benzyl-4-hydroxy-5,6,8,9-tetrahydro-7*H*-pyrimido-[4,5-d]azepine (IVe).* A suspension of 0.5 g of IVc in 2 m*l* of acetic anhydride was heated on a steam bath for 10 min. The precipitate was then collected and recrystallized from methanol, giving 0.4 g (68%) of IVe as colorless prisms; mp 238°C. The analytical sample was dried at 20°C/20 mmHg.

Found: C, 65.37; H, 6.45; N, 17.94%. Calcd for $C_{17}H_{20}N_4O_2$: C, 65.01; H, 6.12; N, 17.77%. ν_{max}^{KBr} 3120 br, 1645 sbr, 1600 s, 1545 sbr, 1391, 1336, 1309, 1240, 1217, 1166 br, 1122, 941, 850, 792, 765, 737, and 692 cm^{-1}.

*7-Benzyl-4-hydroxy-5,6,8,9-tetrahydro-7*H*-pyrimido[4,5-d]azepine (IVf).* To a solution of 6.8 g of IVa in 120 m*l* of 28% aqueous ammonia and 600 m*l* of water were added *ca.* 18 g of freshly-prepared, wet Raney nickel W-2; the mixture was then refluxed for 2 hr. The catalyst was separated while hot and extracted with boiling water. The extract and the filtrate were combined and evaporated *in vacuo*. The recrystallization of the residue from methanol gave 4.8 g of IVf as colorless needles; mp 169—170°C. The concentration of the filtrate afforded a further solid, which was recrystallized from the same solvent to give 0.3 g of the product; mp 167—169°C (total yield, 85%).

Found: C, 70.12; H, 6.38; N, 16.37%. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46%. ν_{max}^{KBr} 2800 sbr, 1600 sbr, 1605 s, 1432, 1358 s, 1317, 1240, 1205, 1161, 1128, 979, 967 s, 925, 871, 739 s, and 706 cm^{-1}.

*7-Benzyl-4-chloro-5,6,8,9-tetrahydro-7*H*-pyrimido[4,5-d]azepine (IVg).* To a solution of 2.5 g of IVf previously dried for 1 hr at 80°C/20 mmHg in 30 m*l* of boiling phosphoryl chloride was added 1.0 m*l* (0.6 equiv) of diethylaniline during 1—2 min; the mixture was then refluxed for 2 hr. After the solvent had been removed *in vacuo*, 10 m*l* of cold water was added to the residue, and the mixture was stirred at 5°C until it became a solution (30 min). Enough solid sodium carbonate (*ca.* 1.8 g) was slowly stirred into the above ice-cooled solution, and then 30 m*l* of chloroform were added. After having been stirred for 15 min at 5°C, the aqueous layer was separated and extracted with chloroform (3×10 m*l*). The combined organic layer was dried over anhydrous potassium carbonate and evaporated *in vacuo*, and the residue was briefly boiled with 10 m*l* of benzene. After cooling, the precipitate was collected, washed with a small amount of benzene, and recrystallized from 10 parts of methanol, giving 1.7 g of IVg hydrochloride as colorless needles; mp 217—218°C. On concentration, the methanolic filtrate yielded an additional solid, which was recrystallized from the same solvent to give 0.6 g of the product; mp 218—219°C (total yield, 76%). The material is soluble only with difficulty in benzene, and slightly soluble in chloroform, methanol, and ethanol. Two more recrystallizations from methanol and drying at 100°C/20 mmHg gave an analytical specimen; mp 220°C.

Found: C, 58.35; H, 5.64; N, 13.99%. Calcd for $C_{15}H_{16}ClN_3\cdot HCl$: C, 58.07; H, 5.53; N, 13.55%. ν_{max}^{Nujol} 2520 sbr, 1560, 1537 s, 1430 s, 1415, 1383 s, 1320, 1290, 1205, 1080, 953, 917 s, 820 s, 780, 753 s and 705 cm^{-1}.

A mixture of 10 m*l* of 10% aqueous sodium carbonate and 1.75 g of the above crude hydrochloride was stirred for 15 min at 5°C. The mixture was then stirred with 30 m*l* of benzene for 10 min at the same temperature. The aqueous layer was extracted with benzene (3×15 m*l*), and the combined benzene layer, after being clarified by filtration, was evaporated *in vacuo* below 40°C (bath temp.), giving 1.48 g (96%) of the free base (IVg) as an almost colorless crystalline powder; mp 66—67.5°C. The material is easily soluble in ethanol, chloroform, and benzene, and slightly soluble in water. It sublimes at 100°C (bath temp.)/0.2 mmHg with a slight decomposition. The analytical specimen, twice recrystallized from light petroleum (30—70°C) and dried at 25°C/20 mmHg, consisted of colorless prisms; mp 67—68°C.

Found: C, 65.83; H, 5.60; N, 15.41%. Calcd for $C_{15}H_{16}ClN_3$: C, 65.80; H, 5.89; N, 15.35%. ν_{max}^{Nujol} 1555 s, 1540 s, 1498, 1450, 1381 s, 1370 s, 1355 s, 1342, 1335 s, 1310, 1292, 1160, 1121 s, 1000, 970, 950, 830, 819, 799, 741 s, and 705 cm^{-1}.

*7-Benzyl-4-methoxy-5,6,8,9-tetrahydro-7*H*-pyrimido[4,5-d]azepine (IVh).* A solution of 0.15 g of IVg in 5 m*l* of absolute methanol and another solution of 0.02 g (1.3 equiv) of sodium in 5 m*l* of the methanol were mixed and boiled for 1 hr. The solvent was evaporated *in vacuo*, and the residue was extracted with boiling benzene (3×5 m*l*). The evaporation of the solvent below 50°C under reduced pressure left 0.12 g (80%) of the crude product as a colorless liquid which did not solidify at −20°C. ν_{max}^{neat} 2980, 2910, 2860, 2765, 1575 sbr, 1555 s, 1460 sbr, 1380 s, 1350, 1338, 1305, 1190, 1168, 1155, 1138, 1080 s, 1039, 946, 860, 801, 781, 740 s, 700 s, 677, and

660 cm^{-1}.

The *picrate*: yellow leaflets (from methanol), mp 207—208°C (reddened). Drying at 20°C/20 mmHg gave an analytical sample.

Found: C, 46.25; H, 3.38; N, 17.62%. Calcd for $C_{16}H_{19}N_3O \cdot 2C_6H_3N_3O_7$: C, 46.22; H, 3.46; N, 17.33%. ν_{max}^{Nujol} 2550 br, 1625 sbr, 1605 sbr, 1560 sbr, 1540 sbr, 1515, 1480 sbr, 1455 sbr, 1430, 1388 s, 1361 s, 1330 sbr, 1295, 1265 sbr, 1143, 1111, 1080, 1041, 940, 910, 891, 789, 768, 746, and 710 s cm^{-1}.

4-Amino-7-benzyl-5,6,8,9-tetrahydro-7H-pyrimido[4,5-d]azepine (IVi). A solution of 0.10 g of IVg in 5 m*l* of ethanolic ammonia saturated at 0°C was heated in a sealed tube at 110°C for 2 hr, and then at 130°C for 8 hr. After the evaporation of the solvent *in vacuo*, the residue was stirred with 1 m*l* of 10% aqueous sodium carbonate. The precipitate was collected and recrystallized from benzene, giving 0.07 g (75%) of IVi as colorless fine prisms. One more recrystallization from the same solvent gave the analytical specimen as colorless leaflets; mp 200.5°C. The material is soluble in chloroform and ethanol, but soluble only with difficulty in water.

Found: C, 70.60; H, 6.87; N, 21.85%. Calcd for $C_{15}H_{18}N_4$: C, 70.83; H, 7.13; N, 22.03%. ν_{max}^{Nujol} 3355, 3170, 1663 s, 1583 s, 1550, 1420, 1380, 1343, 1316, 1262, 1168, 1151, 1130, 978, 951, 874, 801, 780, 740 s, and 700 cm^{-1}. No amination took place when IVg was heated under reflux with concentrated aqueous ammonia.

7-Benzyl-4-hydrazino-5,6,8,9-tetrahydro-7H-pyrimido[4,5-d]azepine (IVj). A mixture of 1.20 g of IVg, 5 m*l* of 80% hydrazine hydrate, and 40 m*l* of ethanol was refluxed for 2 hr. The solvent was then evaporated *in vacuo*, and 5 m*l* of water were added to the residue. After the mixture had been stirred for 5 min at 20°C, the precipitate was collected on a filter and washed with 1 m*l* of cold water, giving 1.12 g (95%) of IVj as a colorless powder; mp 162—165°C. Two recrystallizations from methanol gave an analytically-pure material as colorless plates, mp 165.5—166.5°C; this material is moderately soluble in methanol and ethanol, and slightly soluble in water and benzene.

Found: C, 67.09; H, 7.11; N, 26.11%. Calcd for $C_{15}H_{19}N_5$: C, 66.89; H, 7.11; N, 26.00%. ν_{max}^{Nujol} 3295 s, 3165, 1660, 1595 sbr, 1498 s, 1420 s, 1362, 1350 s, 1340 s, 1323, 1262, 1210, 1168, 990, 985, 961 s, 871, 810, 791, 751, 736 and 706 cm^{-1}. The reaction at 40°C recovered the starting material.

7-Benzyl-5,6,8,9-tetrahydro-7H-pyrimido[4,5-d]azepine (IVk). A suspension of 0.45 g of IVj and 3.5 g of freshly-prepared silver oxide in 30 m*l* of absolute ethanol was refluxed for 2 hr with stirring. The hot mixture was filtered, and the filtrate was treated with carbon. The solvent was evaporated *in vacuo*, and the residue was sublimed at 130°C (bath temp.)/0.1 mmHg, giving 0.33 (83%) of IVk as colorless prisms. Recrystallization from light petroleum (30—70°C) and drying at 25°C/20 mmHg gave an analytical specimen as colorless plates; mp 66.5—67.5°C. The material is soluble in most organic solvents, but soluble only with difficulty in water.

Found: C, 75.85; H, 7.14; N, 17.96%. Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56%. ν_{max}^{Nujol} 1580, 1555, 1410, 1398, 1375, 1359 s, 1312, 1128, 990, 951, 790, 746 s, and 706 cm^{-1}.

The *picrate* was obtained when IVk was added to an ethanolic solution of picric acid (2.1 equiv). It was recrystallized from ethanol and dried at 107°C/20 mmHg to give an analytical sample as yellow prisms; mp 170—171°C.

Found: C, 53.16; H, 4.10; N, 18.25%. Calcd for $C_{15}H_{17}N_3 \cdot C_6H_3N_3O_7$: C, 53.84; H, 4.30; N, 17.94%. ν_{max}^{Nujol} 2700 br, 2570 br, 1620 sbr, 1610 sbr, 1580, 1550 sbr, 1485, 1435, 1403, 1368 s, 1335 sbr, 1310 sbr, 1270 sbr, 1163, 1080, 907 s, 798, 776, 755, and 712 cm^{-1}.

5,6,8,9-Tetrahydro-7H-pyrimido[4,5-d]azepine (Va). A mixture of 0.20 g of IVk, 1 m*l* of acetic acid, and 20 m*l* of ethanol was shaken with hydrogen in the presence of 0.10 g of 10% palladium charcoal until the absorption of hydrogen ceased. The solid was then removed by filtration and washed with hot ethanol. The filtrate and the washings were combined and evaporated *in vacuo*. The residual liquid was suspended in 6 m*l* of 10% aqueous potassium carbonate and extracted with chloroform (3×7 m*l*). The dried extract was freed from the solvent at 60°C (bath temp.)/20 mmHg, giving 0.10 (80%) of Va as a colorless liquid. No crystallization occurred even at −20°C.

The oil was characterized by the *picrate*; yellow needles (from ethanol); mp 224°C (decomp.),.

Found: C, 44.56; H, 3.66; N, 22.00%. Calcd for $C_8H_{11}N_3 \cdot C_6H_3N_3O_7$: C, 44.45; H, 3.73; N, 22.22%. ν_{max}^{Nujol} 2580 br, 2450, 1635 s, 1608 sbr, 1545 sbr, 1480 br, 1450 sbr, 1397 s, 1365 sbr, 1310 sbr, 1270 sbr, 1162 s, 1152, 1079 s, 1026, 928, 912, 839, 780, 743, 721 s, and 710 s cm^{-1}.

7-Benzyl-4-chloro-2-methyl-5,6,8,9-tetrahydro-7H-pyrimido[4,5-d]azepine (IVl). This was prepared as in the case of IVg; the crude product (77%) was obtained as a pale yellow liquid. When purified by distillation, it gave pure IVl in a 30% yield as a colorless liquid, bp 170°C/0.7 mmHg, which crystallized in part.

Found: C, 67.81; H, 6.48; N, 15.05%. Calcd for $C_{16}H_{18}ClN_3$: C, 66.77; H, 6.30; N, 14.60%. ν_{max}^{neat} 2890 s, 2795, 2522, 2480, 1605, 1560 sbr, 1520 sbr, 1492, 1450 s, 1415 sbr, 1400 s, 1361, 1346, 1312 br, 1277 s, 1162, 1128, 1072, 1026, 942 s, 920, 908, 890, 829, 822, 790, 775, 750, 740, 721, and 698 s cm^{-1}.

7-Benzyl-4-hydrazino-2-methyl-5,6,8,9-tetrahydro-7H-pyrimido-[4,5-d]azepine (IVm). The procedure was similar to that used for IVj, except that benzene was used as the recrystallization solvent. The crude chloropyrimido-azepine (IVl) gave IVm as a colorless crystalline powder, mp 124—125°C, in an 87% yield. The material is easily soluble in methanol, ethanol, ethyl acetate, and chloroform, moderately soluble in benzene, and soluble only with difficulty in water. Drying at 60°C/20 mmHg gave an analytical sample.

Found: C, 68.60; H, 7.89; N, 25.42%. Calcd for $C_{16}H_{21}N_5$: C, 67.81; H, 7.47; N, 24.72%. ν_{max}^{Nujol} 3280 sbr, 3230 sbr, 3190 s, 1668, 1575 sbr, 1490 s, 1440 s, 1409 s, 1380, 1348, 1304, 1212, 1169, 1020, 970, 949 s, 797, 775, 760, 730, 700 s, and 660 cm^{-1}.

7-Benzyl-2-methyl-5,6,8,9-tetrahydro-7H-pyrimido[4,5-d]azepine (IVn). This was prepared in a 63% yield from IVm by much the same procedure as that used in preparing IVk. It was a colorless, viscous liquid, bp 155—156°C/0.20 mmHg, which did not crystallize on storage at −20°C.

The material gradually become a yellow viscous liquid in the air, while under ultraviolet light at 254 mμ, it was quickly destroyed and gave a substance which exhibited a blue fluorescence.

Found: C, 75.82; H, 7.79; N, 16.21%. Calcd for $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.59%. ν_{max}^{neat} 2980, 2880, 2855, 1579 s, 1563 sbr, 1495, 1450 sbr, 1445 sbr, 1402, 1372, 1345, 1272, 1163, 1120 br, 1031, 993, 968, 950 sbr, 782, 750 s, 725 and 701 cm^{-1}.

The *picrate*, yellow leaflets (from ethanol); mp 192.5—194°C (melted with darkening).

Found: C, 47.24; H, 3.87; N, 17.29%. Calcd for $C_{16}H_{19}N_3 \cdot 2C_6H_3N_3O_7$: C, 47.26; H, 3.54; N, 17.72%. ν_{max}^{Nujol} 2580 br, 1620 sbr, 1605 sbr, 1562 s, 1550 sbr, 1520, 1490, 1460 br, 1427, 1362 s, 1315 sbr, 1263 sbr, 1160, 1080, 900, 789, 760, 748, and 711 cm^{-1}.

The *hydrochloride* was obtained as a colorless crystalline

powder, mp 240—242°C (from methanol), when dry hydrogen chloride was passed through a solution of IVn in dry ether.

Found: C, 58.75; H, 6.50; N, 12.78%. Calcd for $C_{16}H_{19}N_3 \cdot 2HCl$: C, 58.90; H, 6.49; N, 12.88%. ν_{max}^{KBr} 2960, 2440 sbr, 2080, 1975 br, 1620, 1609 s, 1465, 1452 s, 1410, 1388, 1374, 1311, 1270, 1212, 1148, 1065 br, 1048, 1022, 971, 960, 932, 898 s, 790, 780, 753 s, 729, 710, and 698 cm^{-1}.

1-Acetylpiperid-4-one. A mixture of 20.0 g of piperid-4-one hydrochloride,[6] 30.0 g (2.0 equiv) of acetic anhydride and 220 m*l* of pyridine was heated under reflux for 2 hr. After cooling, 250 m*l* of water were added and the mixture was heated on a steam bath for 30 min and then concentrated to *ca.* 50 m*l* below 60°C (bath temp.) under reduced pressure. To this were added 20 m*l* of 10% aqueous sodium hydrogen carbonate and enough solid sodium hydrogen carbonate (*ca.* 6 g) to pH 7, after which the contents were thoroughly extracted with chloroform (6×50 m*l*). The combined extract was washed once with saturated aqueous sodium chloride and dried over anhydrous potassium carbonate. After the solvent had been removed, the residue was distilled to give 16.2 g (78%) of the acetylpiperidone as a colorless liquid; bp 122—125°C/0.20 mmHg. ν_{max}^{neat} 3450 br, 2960, 2890, 1735 sbr, 1715 sbr, 1660 s, 1640—1620 sbr, 1450—1420 sbr, 1362, 1349, 1310, 1260, 1230 sbr, 1140, 1032, 978, and 758 cm^{-1}

The liquid was identified by the 2,4-*dinitrophenylhydrazone* (yellow fine needles, 80% yield); mp 209—210°C.

Found: C, 48.72; H, 4.96; N, 21.35%. Calcd for $C_{13}H_{15}N_5O_5$: C, 48.59; H, 4.71; N, 21.80%.

1-Acetyl-5-ethoxycarbonyl-1-azacycloheptan-4-one (IIIb). The procedures of Moriya *et al.*[4] were followed. The treatment of 7.06 g of the above acetylpiperidone with 7.81 g (1.1 equiv) of freshly-distilled boron trifluoride and 17.1 g (3.0 equiv) of ethyl diazoacetate gave 7.35 g (65%) of IIIb as a pale yellow, voscous oil; bp 154°C/0.28 mmHg.

Found: C, 57.84; H, 7.78; N, 5.98%. Calcd for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16%. ν_{max}^{neat} 2950 br, 1750 sbr 1710 sbr, 1645 sbr, 1480, 1455 br, 1425 br, 1370, 1315, 1295, 1230 br, 1195 sbr, 1100, 1025, 989 and 896 cm^{-1}.

7-Acetyl-4-hydroxy-2-mercapto-5,6,8,9-tetrahydro-7H-pyrimido[4,5-d]azepine (Vb). The procedure was essentially the same as that used for the benzyl compound IVa, but a slight modification was employed. To a cold solution of 0.40 g (1.5 equiv) of sodium in 70 m*l* of absolute ethanol was added a solution of 9.08 g of IIIb in 30 m*l* of absolute ethanol, and then 3.80 g (1.25 equiv) of finely-powdered thiourea. The mixture was shaken at room temperature until the thiourea had been almost completely dissolved (5 min), and then it was refluxed for 9 hr with stirring. The solvent was removed *in vacuo*, and the residue was dissolved in 20 m*l* of cold water and filtered. The filtrate was brought to pH 4 with 6N hydrochloric acid under cooling and kept at 5°C for two days to give 6.8 g of a precipitate. The concentration of the filtrate to *ca.* 10 m*l* yielded 1.8 g of the same material. Recrystallization from 50% aqueous ethanol gave 6.6 g (69%) of Vb as an almost colorless crystalline powder; mp 286—287°C. One more recrystallization from the same solvent raised the melting point to 288—289°C, and subsequent drying at 100°C/20 mmHg gave an analytical sample.

Found: C, 49.42; H, 5.41; N, 17.07%. Calcd for $C_{10}H_{13}N_3O_2S$: C, 50.18; H, 5.47; N, 17.54%. ν_{max}^{Nujol} 3120 br, 1660 sbr, 1610 sbr, 1550 sbr, 1425 sbr, 1340, 1276, 1212 s, 1198 s, 1121, 926 br, and 762 cm^{-1}.

7-Acetyl-4-hydroxy-2-methyl-5,6,8,9-tetrahydro-7H-pyrimido[4,5-d]azepine (Vc). A mixture of 2.27 g of IIIb, 0.70 g (1.2 equiv) of acetamidine hydrochloride, and 0.60 g (2.6 equiv) of sodium was similarly refluxed in 40 m*l* of absolute ethanol. After being changed to pH 4 with hydrochloric acid, the reaction mixture was well extracted with chloroform (5×10 m*l*). The combined and dried (over anhydrous potassium carbonate) extract was evaporated *in vacuo*, and the residue was recrystallized from ethanol to give 0.80 g (36%) of Vc as a colorless crystalline powder; mp 250—252°C. Two more recrystallizations from the same solvent afforded colorless needles, mp 254—255°C, an aliquot of which was then dried at 160°C/15 mmHg to give an analytical sample.

Found: C, 60.31; H, 7.07; N, 19.06%. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99%. The material dried below 120°C/20 mmHg still possessed the ethanol of crystallization. ν_{max}^{Nujol} 3070 br, 2760, 1660 sbr, 1590 sbr, 1455 sbr, 1425 s, 1380, 1337, 1294, 1282, 1251, 1219, 1201, 1144, 1045, 1037, 1030, 990, 943 s, 900, 795, and 734 cm^{-1}.

7-Acetyl-4-hydroxy-5,6,8,9-tetrahydro-7H-pyrimido[4,5-d]azepine (Vd). This was prepared according to the procedure described for IVf. The treatment of 2.0 g of Vb with 6.0 g of wet Raney nickel W-2, followed by the recrystallization of the crude product from ethanol, gave 1.5 g (87%) of Vd as colorless leaflets; mp 212—213°C. The material is easily soluble in water.

Found: C, 57.94; H, 6.17; N, 20.17%. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28%. ν_{max}^{Nujol} 3050 br, 2700, 1660 sbr, 1630, 1595 sbr, 1551, 1465 sbr, 1380 s, 1275, 1250, 1223, 1192, 1033, 997, 952, 937 s, 919, 864, 812, 785, and 665 br cm^{-1}.

4-Hydroxy-5,6,8,9-tetrahydro-7H-pyrimido[4,5-d]azepine (Ve). A solution of 0.20 g of Vd in 4 m*l* of 6N hydrochloric acid was refluxed for 4 hr. The solvent was removed under reduced pressure below 60°C (bath temp.), and the residue was boiled with 5 m*l* of ethanol. The precipitate was recrystallized from a mixture of N HCl–EtOH (1:30) to give 0.20 g (97%) of fine, colorless needles; mp 272—275°C (gradual decomp.). Likewise, one more recrystallization gave an analytical specimen; mp 272—274°C (foaming). The hydrochloride contained the water of crystallization, which was lost on drying above 110°C. Drying at 140°C/20 mmHg gave an analytical sample. It is very soluble in water and 10% aqueous sodium hydrogen carbonate.

Found: C, 46.71; H, 5.89; N, 20.52%. Calcd for $C_8H_{11}N_3O \cdot HCl$: C, 47.64; H, 6.00; N, 20.84%. ν_{max}^{Nujol} 3100—2400 br, 1650 sbr, 1630 sbr, 1605 s, 1595 s, 1552, 1450 sbr, 1428, 1403, 1373, 1308, 1250, 1230, 1180, 1129, 1101, 989, 976, 943 s, 890, 861, 831, and 795 cm^{-1}.

The *picrate*; yellow prisms (from 80% aqueous ethanol); mp 117—119°C. The analytical sample was dried at 60°C/20 mmHg.

Found: C, 36.09; H, 3.02; N, 18.98%. Calcd for $C_8H_{11}N_3O \cdot 2C_6H_3N_3O_7 \cdot HCl$: C, 36.40; H, 2.75; N, 19.10%. ν_{max}^{Nujol} 3470, 3230, 3070, 1685 s, 1675, 1630 s, 1615 s, 1565 sbr, 1540, 1465 sbr, 1383, 1373 s, 1355 s, 1335 s, 1303, 1284 s, 1172, 1098, 920, 863, 792, 750, and 720 br cm^{-1}.

A solution of 0.10 g of the hydrochloride in 10 m*l* of water was passed through a column of the Amberlite CC-413 and eluted with water. The eluate (*ca.* 80 m*l*) was evaporated *in vacuo*, giving the free base Ve as an almost colorless powder; this powder gradually melted at about 220°C. The material was very hygroscopic and became a pale yellow viscous tarry oil on being set aside in the air; thus, it was not analyzed. However, the NMR spectrum is shown in Table 1. It is very soluble in water, and slightly so in ethanol, but insoluble in chloroform.

4-Mercapto-7-thioacetyl-5,6,8,9-tetrahydro-7H-pyrimido[4,5-d]azepine (Vf). A mixture of 0.10 g of Vd and 2 m*l* of pyridine was heated at 110°C. After the resultant solution

6) A. Yokoo and S. Morosawa, This Bulletin, **29**, 631 (1956).

had been cooled to 90°C, 0.20 g (2.0 equiv) of powdered phosphoryl pentasulfide was added over a 1-min period and the mixture was heated under reflux for 30 min. The reaction mixture was treated with 2 m*l* of water and evaporated *in vacuo* at 60°C. The residue was stirred with 1 m*l* of water under cooling, and the precipitate was collected and recrystallized twice from ethanol to give 0.075 g (71%) of Vf as a yellow crystalline powder; mp 247—248°C (blackened). The drying of an aliquot of the powder at 140°C/20 mmHg afforded the analytical sample.

Found: C, 49.96; H, 5.32; N, 17.38%. Calcd for $C_{10}H_{13}N_3S_2$: C, 50.18; H, 5.47; N, 17.56%.