Reactions of 4-(2-Hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic Acid with Acetic Anhydride. Syntheses of 8,9-Dihydro-6a-methyl-2-phenyl-5*H*,6a*H*-oxazolo-[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazin-5-one and 8,9-Dihydro-8,8-dimethyl-2-phenyl-5*H*-oxazolo[2′,3′:6,1]pyrido[2,3-*d*]pyrimidin-5-one

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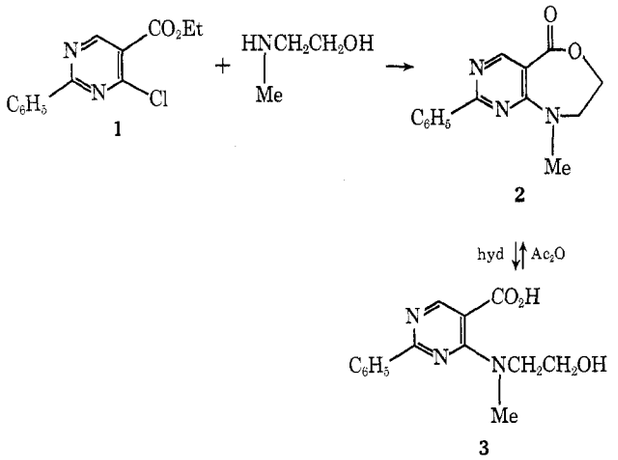
8,9-Dihydro-6a-methyl-2-phenyl-5*H*,6a*H*-oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazin-5-one (**7a**), the first member of a new heterocyclic system, oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazine, was obtained from the reaction of 4-(2-hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**5a**) with acetic anhydride. The reaction of 5-carboethoxy-4-chloro-2-phenylpyrimidine and 2-hydroxyethylamine, and subsequent hydrolysis, afforded **5a**. Additional members of the new ring system, **7b–e**, were prepared in an analogous fashion. 8,9-Dihydro-8,8-dimethyl-2-phenyl-5*H*-oxazolo[2′,3′:6,1]pyrido[2,3-*d*]pyrimidin-5-one (**11**) was the main product of the reaction of 4-(2-hydroxy-2-methylpropylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**10**) with acetic anhydride. Possible reaction mechanisms for the formation of the new compounds were discussed.

In a previous paper[1] we described the synthesis of a new heterocyclic class, the pyrimido[4,5-*e*][1,4]-oxazepin-5-ones, made directly from 5-carboethoxy-4-chloropyrimidines and 2-(N-substituted)aminoethanols. Further investigation in this area led us to prepare a number of novel compounds which represent new ring systems, *i.e.*, the oxazolo[2,3-*b*]pyrimido[4,5-*d*][1.3]oxazines and oxazolo[2′,3′:6,1]pyrido[2,3-*d*]-pyrimidines. This paper describes the syntheses of such compounds and possible reaction mechanisms for their formation.

Contrary to our previous observation that the 2-(N-substituted)aminoethanols reacted smoothly with 5-carboethoxy-4-chloro-2-phenylpyrimidine (**1**) in refluxing ethanol to give the corresponding 9-substituted 8,9-dihydro-2-phenylpyrimido[4,5-*e*][1,4]oxazepin-5-(7*H*)-one[1] such as **2** (Scheme I), the 2-(N-unsubstituted)-

SCHEME I



aminoethanols such as 2-aminoethanol failed to give a cyclized product under similar conditions, but instead afforded only the corresponding open-chain compound, 5-carboethoxy-4-(2-hydroxyethylamino)-2-phenylpyrimidine (**4a**). Neither extension of the reaction time nor elevation of the reaction temperature was effective in bringing about the cyclization.[2] The inability of **4a** to cyclize may be due to an unfavorable steric relationship of the hydroxyl group relative to the ester carbonyl, which is held by the amino hydrogen through intramolecular hydrogen bonding.

As an alternative route for the cyclization, we turned our attention to the reaction of 4-(2-hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**5a**) with acetic anhydride. Such a ring closure was readily effected in the case of 4-[(2-hydroxyethyl)methylamino]-2-phenyl-5-pyrimidinecarboxylic acid (**3**). Thus, treatment of **3** with acetic anhydride under refluxing conditions gave **2** in 66% yield. Saponification of **4a** with dilute aqueous sodium hydroxide solution and subsequent acidification afforded the corresponding pyrimidinecarboxylic acid **5a**. However, the treatment of **5a** with acetic anhydride under conditions similar to those used for the preparation of **2** resulted in the isolation, not of **6a**, but of 8,9-dihydro-6a-methyl-2-phenyl-5*H*,6a*H*-oxazolo[2,3-*b*]pyrimido-[4,5-*d*][1,3]oxazin-5-one (**7a**),[3] as shown by the elemental analyses and spectral data. The infrared spectrum of **7a** showed only one absorption band at 5.80 μ in the carbonyl region. The nmr spectrum showed the methyl proton signal at δ 1.77 ppm, in support of the tricyclic structure. The nmr signal for the methyl protons in **6a** would be expected to appear in the region of δ 2.0–2.2 ppm.[4] Other proton signals of **7a** were a multiplet at δ 5.15 (4 H), which was attributed to the protons of the ethylene linkage; an aromatic multiplet centered at 7.70 (3 H) and 6.50 (2 H); and a pyrimidine proton at 9.17 ppm. In the presence of acid or base, **7a** was rapidly hydrolyzed, giving back the starting material **5a**. To our best knowledge, **7a** represents the first example of the oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazine ring system. Several other examples of this new heterocyclic system (**7b–e**) were similarly prepared, as shown in Scheme II.

A plausible mechanism of the cyclization appears to involve intermediates **8** and **9**. Initial acetylation on the hydroxy and the carboxylic acid groups of **5** forms

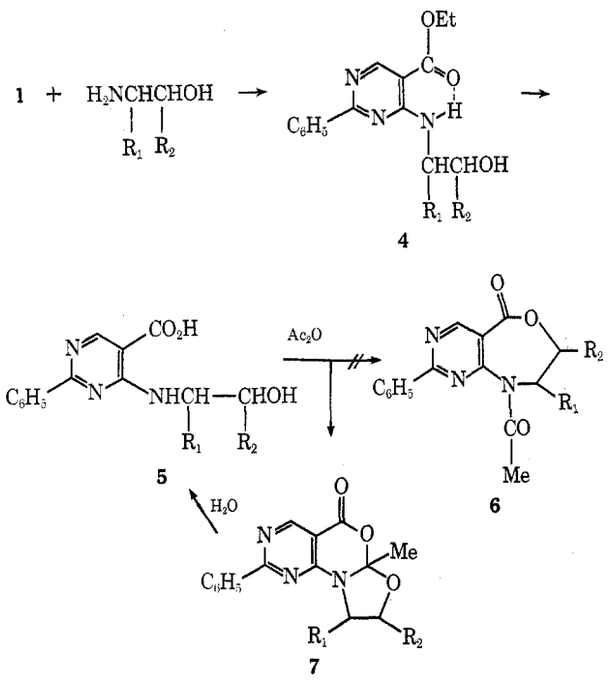
(1) A. A. Santilli, D. H. Kim, and S. V. Wanser, *J. Heterocycl. Chem.*, **9**, 309 (1972).

(2) After submission of our manuscript, there appeared a paper which described an observation similar to ours: S. Yunugi, M. Hieda, T. Fushima, and M. Tomimoto, *Chem. Pharm. Bull.*, **19**, 2354 (1971).

(3) This structure was suggested by Dr. S. C. Bell of these laboratories, to whom the authors are indebted.

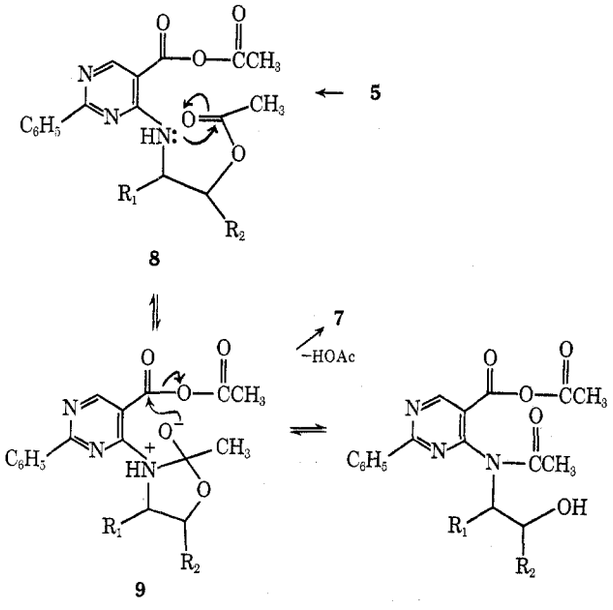
(4) Unpublished result obtained by D. H. Kim.

SCHEME II



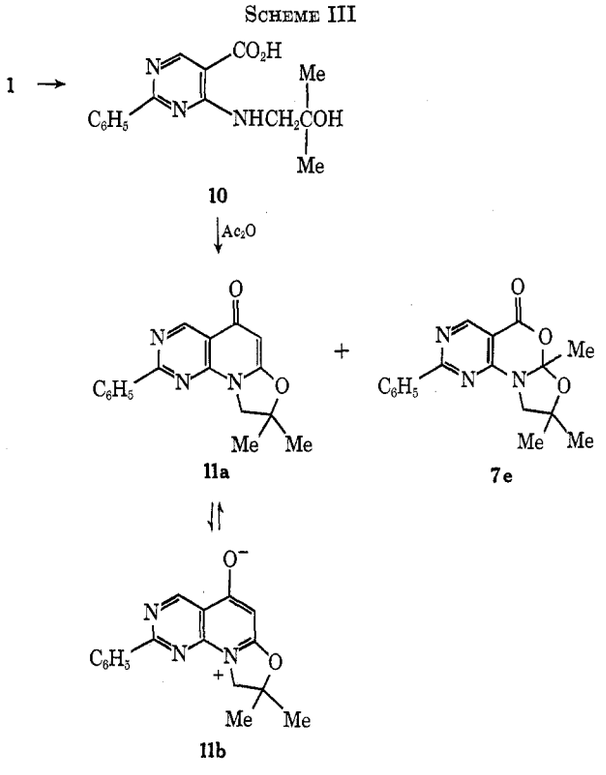
a, $R_1 = H; R_2 = H$
b, $R_1 = H; R_2 = Me$
c, $R_1 = H; R_2 = o$-chlorophenyl
d, $R_1 = Et; R_2 = H$

8. An intramolecular nucleophilic attack by the C_4-amino group in **8** on the *O*-acetyl carbonyl group generates **9**. An intermediate such as **9** has been postulated by Amundsen and Ambrosio for the process of O to N migration of an acyl group in *o*-aminophenyl esters.[5] Subsequent intramolecular nucleophilic attack on the anhydride carbonyl group by the newly generated nucleophilic center in **9** affords the product **7** with elimination of acetate ion.[6] In support of the proposed mechanism, treatment of 4-(2-hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide with acetic anhydride under similar conditions failed to cause cyclization, but afforded, instead, 4-(2-acetoxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide.



Interestingly, cyclization of 4-(2-hydroxy-2-methylpropylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**10**) with acetic anhydride took still another reaction course. Thus when **10**, which was prepared from **1** and 2-hydroxy-2-methylpropylamine by the method described earlier in this paper, was allowed to react with a large excess of acetic anhydride for 1 hr under reflux, 8,9-dihydro-8,8-dimethyl-2-phenyl-5*H*-oxazolo-[2′,3′:6,1]pyrido[2,3-*d*]pyrimidin-5-one (**11**), the first example of another new ring system, was isolated in a yield of 49%, along with a very small amount of **7e** (Scheme III). The main product analyzed for $C_{17}H_{15}N_3O_2$, which was confirmed by the mass spectral data as shown by $M \cdot^+$ *m/e* 293. The nmr spectrum of **11** (DMSO-d_6) showed, apart from the aromatic proton signals, a 6-methyl proton signal at δ 1.75 as a sharp singlet, a methylene proton signal as a singlet at δ 4.47, and a vinyl proton signal at δ 5.73 as a singlet. The absence of an absorption band in the carbonyl region of the ir spectrum and the downfield shift of the magnetic resonance signal of the methylene protons of **11** compared with that of corresponding protons in **7e** suggests that the product exists as **11b**. In this form it is expected to be thermodynamically more stable in the ground state.

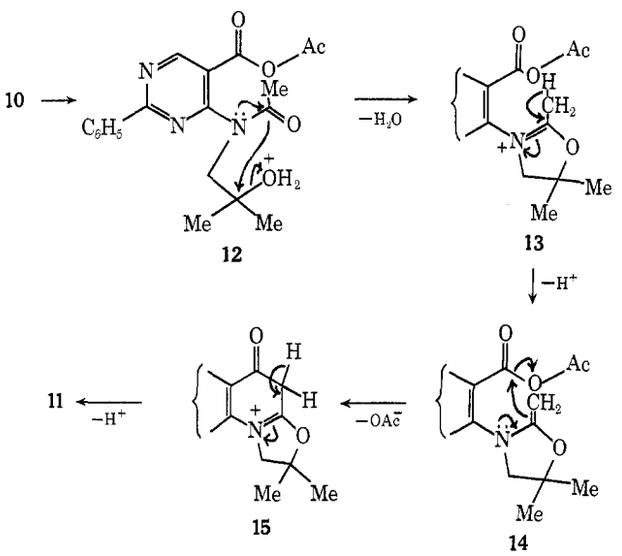
SCHEME III



The formation of **11** from **10** can be envisioned by the sequence shown in Scheme IV. Due to the greatly reduced nucleophilicity of the hydroxy group as being *tert*-carbinol, the initial acetylation now takes place at the C_4-amino nitrogen, with concurrent or stepwise

(5) L. H. Amundsen and C. Ambrosio, *J. Org. Chem.*, **31**, 731 (1966).
(6) Recently a similar mechanism was presented by Bain and Smalley for the formation of 2-substituted 4*H*-3,1-benzoxazin-4-ones from anthranilic acid and benzoyl chloride: D. I. Bain and R. K. Smalley, *J. Chem. Soc. C*, 1593 (1968).

SCHEME IV



formation of a mixed anhydride, to give an intermediate (**12**). Cyclization of the intermediate then follows, with displacement of the hydroxy group, which is protonated by acetic acid generated *in situ*, resulting in formation of an oxazolium salt.[7] The latter then transforms, with loss of a proton, into chemically reactive **14**. The final ring-closure reaction now takes place, with elimination of acetate ion from the mixed anhydride of **14**, by a process resembling an enamine reaction. Subsequent deprotonation of **15** affords the isolated product, **11**.

It is worthy to note that in the nmr spectrum of **7e** (DMSO-d_6) there appeared two broad singlet proton signals at δ 3.85 and 4.22, of equal intensity, both attributed to the methylene protons. When the spectrum was determined at 100°, however, there was only one singlet, which appeared at the midpoint of the two peaks. The broad singlet of the *gem*-dimethyl protons which appeared at δ 1.43 ppm sharpened without change in its position at 100°. A similar phenomenon was observed with **7a**. This observation suggests that 8,9-dihydro-6a-methyl-5*H*,6a*H*-oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazin-5-one (**7a–e**) exists in two difficultly interchangeable conformational states at room temperature.[8]

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained in KBr discs using a Perkin-Elmer 21 spectrophotometer, and nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal reference. Elemental analyses were performed by the analytical section of Wyeth Laboratories, Inc.

5-Carboethoxy-4-(2-hydroxyethylamino)-2-phenylpyrimidine (**4a**).—5-Carboethoxy-4-chloro-2-phenylpyrimidine (**1**) (18 g) was added in small portions to a solution containing 30 ml of 2-hydroxyethylamine in 70 ml of absolute ethanol. Heat was evolved during the addition. The resulting mixture was heated on a steam bath for 7 min. The solvent was removed under reduced pressure, giving an oil which solidified on chilling and scratching. The product weighed 6.0 g and melted at 128–133°. Recrystallization from absolute ethanol increased the melting point to 134–136°; ir 5.90 μ (C=O); nmr ($CDCl_3$) δ 1.33 (t, 3 H, CH_2CH_3), 2.07 (broad s, 1 H, OH), 3.86 (s) and 3.83 (shoulder) (4 H, CH_2CH_2), 4.30 (q, 2 H, CH_2CH_3), 7.47 (m, 3 H, aromatic), 8.39 (m, 3 H, 2 aromatic and NH), and 9.05 ppm (s, 1 H, pyrimidine).

Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.59; H, 5.76; N, 14.77.

5-Carboethoxy-4-(2-hydroxypropylamino)-2-phenylpyrimidine (**4b**) was prepared in the same fashion as **4a** from **1** and 2-hydroxypropylamine in 57% yield, mp 98–100°, ir 5.90 μ (C=O).

Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.95. Found: C, 63.45; H, 6.11; N, 14.00.

5-Carboethoxy-4-(2-*o*-chlorophenyl-2-hydroxyethylamino)-2-phenylpyrimidine (**4c**) was prepared in a similar fashion to **4a** from **1** and 2-(*o*-chlorophenyl)ethanolamine, then recrystallized from absolute ethanol, mp 164–166°, ir 5.93 μ (C=O).

Anal. Calcd for $C_{21}H_{20}ClN_3O_3$: C, 63.40; H, 5.07; N, 10.56; Cl, 8.91. Found: C, 63.55; H, 5.00; N, 10.83; Cl, 8.76.

5-Carboethoxy-4-(1-hydroxymethylpropylamino)-2-phenylpyrimidine (**4d**).—**1** (2.6 g) was added in small portions under mechanical stirring to 12 ml of DMF containing 0.9 g of 2-aminobutanol and 1.0 g of powdered sodium carbonate. After being stirred for 30 min at room temperature, the reaction mixture was heated to boiling for 5 min and then poured into 250 ml of cold water, causing separation of an oil. The aqueous layer was decanted and fresh water was added. The oil solidified on chilling and scratching to give 2.5 g of product, mp 91–100°. Recrystallization from methanol increased the melting point to 103–105°, ir 5.91 μ (C=O).

Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.33. Found: C, 64.75; H, 6.88; N, 13.51.

4-(2-Hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic Acid (**5a**).—**4a** (13 g) was added to a mixture of 20% aqueous NaOH solution (50 ml) and absolute ethanol (20 ml) and the resulting mixture was refluxed for 15 min. Acidification of the reaction mixture with dilute HCl caused separation of a precipitate, which was collected on a filter and washed with water. The product (Table I) weighed 10 g and melted at 244–246° dec, ir 3.85 and 6.05 μ (COOH).

5-Carboethoxy-4-(2-hydroxy-2-methylpropylamino)-2-phenylpyrimidine.—To a solution containing 26 g of 2-hydroxy-2-methylpropylamine in 60 ml of absolute ethanol was added 15 g of **1**, in small portions and with gentle heating and stirring. The resulting mixture was heated on a steam bath for 10 min. After most of the ethanol had been removed under reduced pressure, the concentrated reaction mixture was poured into 300 ml of cold water, whereby an oil separated. Chilling and scratching of the oil caused solidification. The solid material was collected on a filter and washed with water several times, giving 16 g of product, mp 76–87°. Recrystallization of the crude product from petroleum ether (bp 30–60°) raised the melting point to 89.5–92°; ir 5.90 μ (C=O); nmr ($CDCl_3$) δ 1.32 (s, 6 H, CH_3CCH_3), 1.37 (t, 3 H, CH_3CH_2), 3.08 (broad s, 1 H, OH), 3.72 (d, 2 H, $NHCH_2$), 4.38 (t, 2 H, OCH_2), 7.50 (m, 3 H, aromatic), 8.47 (m, 2 H, aromatic), 8.55 (t, 1 H, NH), and 9.00 (s, 1 H, pyrimidine).

Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.33. Found: C, 65.10; H, 6.84; N, 13.53.

4-(2-Hydroxy-2-methylpropylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**10**) was prepared by the hydrolysis of its corresponding ethyl ester in a similar fashion to **5a**: mp 239–241° dec; ir 3.65 and 6.10 μ (COOH); nmr (DMSO-d_6) δ 1.22 (s, 6 H, CH_3CCH_3), 3.68 (d, 2 H, J = 6 Hz, $NHCH_2$), 7.55 (m, 3 H, aromatic), 8.48 (m, 2 H, aromatic), 8.76 (t, 1 H, J = 6 Hz, NH), and 8.92 (s, 1 H, pyrimidine).

Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.45; H, 5.65; N, 14.43.

8,9-Dihydro-9-methyl-2-phenylpyrimido[4,5-*e*][1,4]oxazepin-5(7*H*)-one (**2**).—A mixture of 4-[(2-hydroxyethyl)methylamino]-2-phenyl-5-pyrimidinecarboxylic acid[1] (1.8 g) and acetic anhydride (20 ml) was heated under reflux for 40 min. Most of the excess acetic anhydride was removed by distillation under reduced pressure. Chilling of the concentrated solution in ice caused separation of 1.1 g of crystalline product, mp 161–167°.

(7) Amides of 2-hydroxyethylamines are known to cyclize to oxazolines under acidic conditions. See J. A. Frump, *Chem. Rev.*, **71**, 483 (1971).

(8) One of the referees suggested that the observed nmr changes might be due to ionization of **7e** to its opened zwitterionic form at 100°.

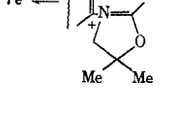


TABLE I

4-(2-HYDROXYETHYLAMINO)-2-PHENYL-5-PYRIMIDINECARBOXYLIC ACIDS[a]

Compd	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
5a	244–246 dec	$C_{13}H_{13}N_3O_3$	60.22	5.05	16.21	60.49	5.29	16.01
5b	241.5–242.5 dec	$C_{14}H_{15}N_3O_3$	61.53	5.53	15.38	61.48	5.24	15.34
5c	238–240 dec	$C_{19}H_{16}ClN_3O_3$	61.71	4.36	11.36	61.63	4.69	11.50
5d	258–261 dec	$C_{15}H_{17}N_3O_3$	62.70	5.96	14.63	62.63	5.94	14.33

[a] Microanalytical results for C, H, and N agreed with theoretical values within ±0.4%.

TABLE II

8,9-DIHYDRO-6a-METHYL-2-PHENYL-5*H*,6a*H*-OXAZOLO[2,3-*b*]PYRIMIDO[4,5-*d*][1,3]OXAZIN-5-ONES[a]

Compd	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
7a	176–179	70	$C_{15}H_{13}N_3O_3$	63.59	4.63	14.83	63.75	4.63	14.86
7b	166–168.5	64	$C_{16}H_{15}N_3O_3$	64.63	5.09	14.14	64.31	4.78	13.93
7c	189–191	80	$C_{21}H_{16}ClN_3O_3$	64.04	4.10	10.67	64.04	4.05	10.74
7d	179–183	12	$C_{17}H_{17}N_3O_3$	65.58	5.50	13.50	65.79	5.51	13.51

[a] Microanalytical results for C, H, and N agreed with theoretical values to within ±0.4%.

Recrystallization from absolute ethanol improved the melting point to 170–173° (lit.[1] mp 170–173°). A mixture melting point with an authentic sample was not depressed.

8,9-Dihydro-6a-methyl-2-phenyl-5*H*,6a*H*-oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazin-5-one (7a).—A mixture of **5a** (1.5 g) and acetic anhydride (30 ml) was heated to obtain a clear solution. The resulting solution was refluxed for 0.5 hr. The excess acetic anhydride was distilled off under reduced pressure, giving an oil which solidified on chilling. The solid was collected on a filter and washed with acetone, yielding 1.1 g of product, mp 176–178°. Recrystallization from acetone afforded an analytical sample.

In a similar fashion, **7b–d** (Table II) were prepared from acetic anhydride and **5b–d**, respectively, and recrystallized from acetic anhydride.

8,9-Dihydro-8,8-dimethyl-2-phenyl-5*H*-oxazolo[2′,3′:6,1]pyrido[2,3-*d*]pyrimidin-5-one (11) and 8,9-Dihydro-6a,8,8-trimethyl-2-phenyl-5*H*,6a*H*-oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazin-5-one (7e).—A mixture of **10** (3.0 g) and acetic anhydride (50 ml) was heated to obtain a clear solution. The resulting solution was refluxed for 0.5 hr, and most of the excess acetic anhydride was distilled under reduced pressure. The concentrated solution was filtered under suction while hot. Chilling of the filtrate caused separation of a crystalline product which was collected on a filter, giving 1.5 g of **11**, mp 243–248°. Recrystallization from acetic anhydride raised the melting point to 251–252°, uv max (95% EtOH) 274 mμ (ε 28.4 × 10³) and 304 (19.2 × 10³).

Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.69 H, 5.22; N, 14.35.

Concentration of the mother liquor under reduced pressure and subsequent chilling in ice caused separation of a small amount of **7e**, which was collected on a filter and recrystallized from acetic anhydride: mp 138–140.5°; ir 5.80 μ (C=O); nmr (DMSO-d_6) δ 1.43 (s, 6 H, CH_3CCH_3), 1.73 (s, 3 H, CH_3), 3.85 and 4.22, which at 100° merged into a singlet at 4.03 (2 H, CH_2), 7.65 (m, 3 H, aromatic), 8.50 (m, 2 H, aromatic), and 9.05 (s, 1 H, pyrimidine).

Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.68; H, 5.50; N, 13.50. Found: C, 65.63; H, 5.21; N, 13.23.

4-(2-Hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide.—A mixture of 10 g of **4a** and 100 ml of methylamine–ethanol solution which was obtained by saturating methylamine in ethanol at room temperature was charged in a steel bomb. The bomb was heated in a steam bath for 5 hr. After the bomb was cooled to room temperature, it was opened. Evaporation of most of the unreacted amine caused separation of 9.1 g of product, mp 206–208°. Recrystallization from absolute ethanol afforded an analytical sample, mp 205–207°, ir 6.12 μ (amide C=O).

Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.88; H, 6.28; N, 20.52.

4-(2-Hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide Acetate Ester.—A mixture of 2.0 g of 4-(2-hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide and 45 ml of acetic anhydride was heated under reflux for 2 hr. Removal of the excess acetic anhydride under reduced pressure afforded a solid residue which was collected on a filter and recrystallized from absolute ethanol, giving 1.0 g of product, mp 147–149°, ir 5.76 (ester C=O) and 6.11 μ (amide C=O).

Anal. Calcd for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.83. Found: C, 61.41; H, 6.01; N, 17.96.

Registry No.—**4a,** 32515-49-4; **4b,** 32412-64-9; **4c,** 32556-42-6; **4d,** 32412-65-0; **5a,** 32412-66-1; **5b,** 32412-67-2; **5c,** 32412-68-3; **5d,** 32412-69-4; **7a,** 32412-72-9; **7b,** 32412-73-0; **7c,** 32412-74-1; **7d,** 32412-75-2; **7e,** 32412-77-4; **10,** 32412-71-8; **11,** 34111-38-1; 5-carboethoxy-4-(2-hydroxy-2-methylpropylamine)-2-phenylpyrimidine, 32412-70-7; 4-(2-hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide, 34922-22-0; 4-(2-hydroxyethylamino)-*N*-methyl-2-phenyl-5-pyrimidinecarboxamide acetate ester, 34922-23-1.