Ring Closure Reaction of 4-(2-Hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic Acid With Acetic Anhydride. Synthesis of Pyrimido[5,4-*c*][1,5]benzoxazepin-5(11*H*)ones.

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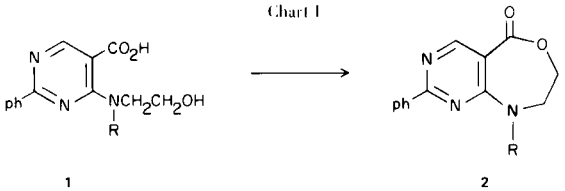
Syntheses of 11-acetyl-2-phenylpyrimido[5,4-*c*][1,5]benzoxazepin-5(11*H*)one (**16a**) and analogs (**16b,c**, **22**) were described. The reaction of 4-chloro-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (**7**) with 2-aminophenol afforded 4-(2-hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (**8a**). The latter was also prepared by catalytic reduction of 4-(2-nitrophenoxy)-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (**9**), which was obtained from **7** and 2-nitrophenol. Involvement of 4-(2-aminophenoxy)-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (**12a**) in this reduction as an intermediate was demonstrated by an independent synthesis of **12a** and its subsequent rearrangement to **8a**. Hydrolysis of **8a** or **12a** gave 4-(2-hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic acid (**15a**). Reaction of **15a** with acetic anhydride afforded **16a**, the first member of a novel ring system, the pyrimido[5,4-*c*][1,5]-benzoxazepin. Additional examples (**16b,c**) were prepared similarly. The corresponding 11-ethyl derivative (**22**) was prepared in similar fashion, starting with **7** and 2-ethylaminophenol. A possible reaction mechanism for the formation of **16a-c** from **15a-c** and acetic anhydride was discussed.

Previously we reported different types of ring closure reactions of 4-(2-hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic acids with acetic anhydride (1). While 4-(*N*-substituted-2-hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**1**, R = alkyl) cyclized to give 9-substituted-8,9-dihydro-2-phenylpyrimido[4,5-*e*][1,4]oxazepin-5(7*H*)ones (**2**) on treatment with refluxing acetic anhydride, the corresponding *N*-unsubstituted pyrimidine derivatives such as **3** cyclized differently to give tricyclic compounds such as 8,9-dihydro-6a-methyl-2-phenyl-5*H*, 6a*H*-oxazolo[2,3-*b*]pyrimido[4,5-*d*][1,3]oxazin-5-one (**4**) under similar conditions. Furthermore, cyclization of 4-(2-hydroxy-2-methylpropylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**5**) with acetic acid took still another course to form 8,9-dihydro-8,8-dimethyl-2-phenyl-5*H*-oxazolo[2′,3′;6,1]pyrido[2,3-*d*]pyrimidin-5-one (**6**) (Chart I).

Chart I



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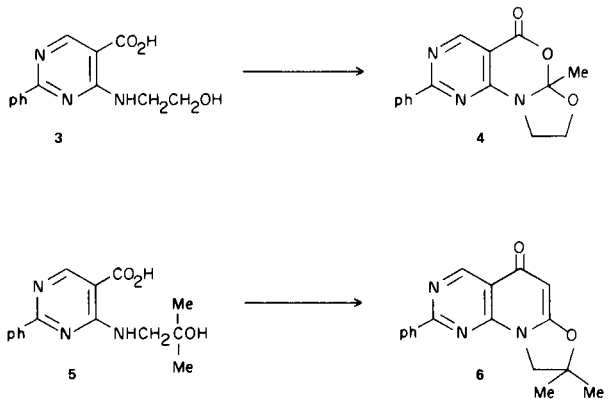


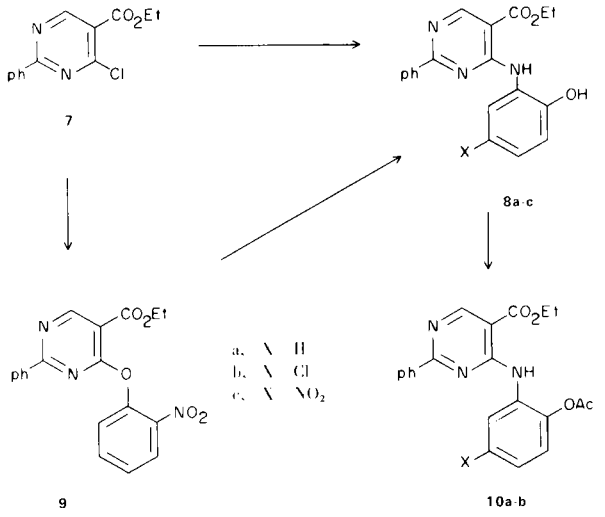
3 4

5 6

As an extention of our work in this area, it was thought to be of interest to examine the cyclization reaction of 4-(2-hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic acid (**15a**) with acetic anhydride. This led us to observe that **15a** takes a cyclization course which is further different from those described earlier (1), giving 11-acetyl-2-phenylpyrimido[5,4-*c*][1,5]benzoxazepin-5(11*H*)one (**16a**). Since this compound was found to be the first example of a heretofore unreported heterocyclic class, we prepared a few additional members of this class for their pharmacological evaluation, and investigated the synthetic route to some extent.

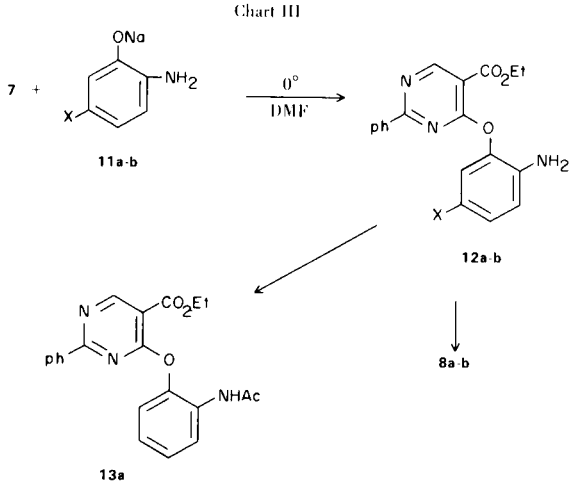
Treatment of 4-chloro-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (**7**) (2) with 2-aminophenol in the presence of sodium ethoxide in boiling ethanol afforded 4-(2-hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (**8a**) in 67% yield (Chart II). The structure of **8a** was supported by its nmr spectral data which showed, apart from the aromatic and ethyl proton signals, a broad singlet for NH at δ 10.17, and a singlet at 10.63 ppm for OH. These signals disappeared on treatment with deuterium oxide. Furthermore, treatment of **8a** with acetic anhydride in pyridine afforded the *O*-acetyl derivative **10a**, the structure of which was supported by its ir carbonyl absorption band at 6.56 μ. In similar fashion **8b-c** were prepared from **7** and corresponding aminophenols.

Chart II



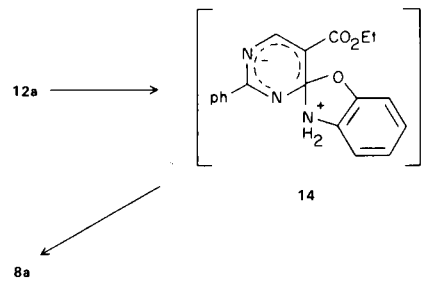
Alternatively, **8a** was prepared by the catalytic reduction of **9** which was obtained by treatment of the sodium salt of 2-nitrophenol with **7** in DMF (3) (Chart II). Reduction of the nitro group of **9** to an amino, giving 4-(2-aminophenoxy)-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (**12a**), and subsequent rearrangement of **12a** under the reaction conditions afforded **8a**. The involvement of **12a** was demonstrated by the independent synthesis of **12a** and the following conversion into **8a** under conditions similar to those used for the hydrogenation. Thus, treatment of the sodium salt of 2-aminophenol with **7** at 0° in DMF afforded **12a**, the ir spectrum of which showed typical primary amino stretching bands at 2.95 and 3.05 μ. The structure of **12a** was further supported by its reaction with acetic anhydride to form the *N*-acetylaminophenoxypyrimidine **13a**, which exhibited its amide carbonyl absorption band at 6.20 μ.

Chart III



The rearrangement of **12a** to **8a** was brought about by warming it in ethanol on a steam bath for 30 minutes. The rearrangement could also be effected by heating **12a** without solvent at about 180° for 15 minutes. The facile rearrangement of **12a** and related compounds under neutral conditions is apparently due to the increased activation at the C_4 position of the pyrimidine nucleus by the presence of a carbethoxy and a phenyl group at the C_5 and C_2 positions, respectively. The rearrangement, which is reminiscent of the Smiles rearrangement (4), must involve an intermediate such as **14** (Chart IV).

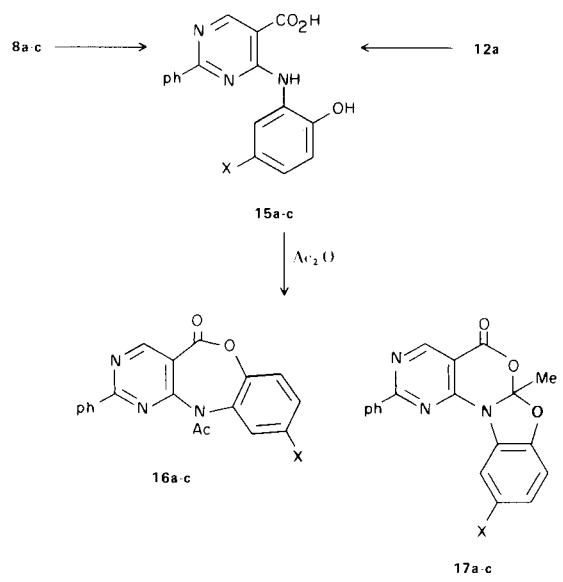
Chart IV



The pyrimidinecarboxylic acid esters **8a-c** were converted into the corresponding acids **15a-c** by saponification with dilute aqueous sodium hydroxide solution followed by acidification with hydrochloric acid. The acid **15a** was also obtainable directly from **12a** by treatment with aqueous base and subsequent acidification, under which conditions the saponification of the ester was accompanied by the Smiles rearrangement.

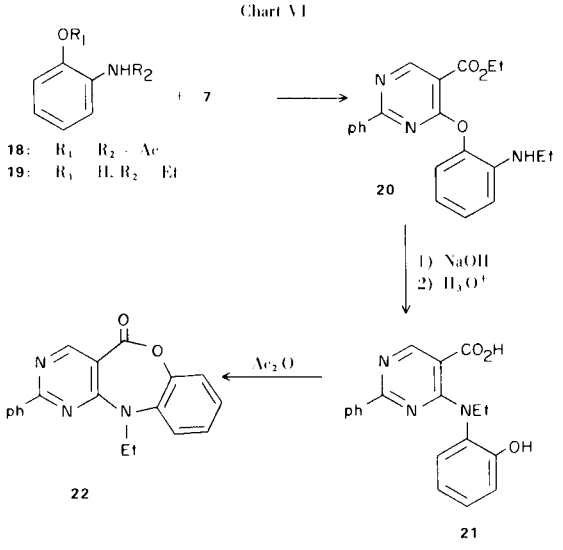
Treatment of **15a** with a large excess of acetic anhydride under refluxing conditions for 45 minutes afforded 11-acetyl-2-phenylpyrimido[5,4-*c*][1,5]benzoxazepin-5(11*H*)-one (**16a**) in 51% yield. The structural assignment was supported by the elemental analysis and spectral data.

Chart V



The product was analyzed for $C_{19}H_{13}N_3O_3$ and showed ir carbonyl absorption bands at 5.72 and 6.20 μ. In the nmr spectrum, one of the protons of the disubstituted benzene ring showed its signal at δ 8.08 ppm as a complex multiplet, differentiated from the signals of the remaining three protons, which appeared as a multiplet at δ 7.13 ppm. The downfield shift of the aromatic signal favors the assigned structure **16a** over the isomeric **17a** (5), since it has been well established that in the nmr spectra of *ortho*-substituted acetylaniline, the proton *ortho* to the acetylamino group experiences an unusually high degree of deshielding effect (6). Additional examples of the new ring system (**16b-c**) were prepared in similar fashion from **15b,c** and acetic anhydride. Further supporting evidence for the assigned structure **16a** was obtained by mass spectral comparison with a model compound, 11-ethyl-2-phenylpyrimido[5,4-c][1,5]benzoxazepin-5(11*H*)one (**22**).

Chart VI



Synthesis of **22** involves treatment of 2-ethylaminophenol (19) with **7** in boiling ethanol for 45 minutes to give 4-(2-ethylaminophenoxy)-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (**20**). Interestingly, this compound failed to rearrange under the conditions used for the rearrangement of the corresponding *N*-unsubstituted-2-aminophenoxy derivative **12a**. This is in agreement with the observation made by Roberts and Clark in their study on the rearrangement of *o*-aminodiphenyl ethers (7). Treatment of **20** with 15% sodium hydroxide solution for 1.5 hours under refluxing conditions followed by acidification with dilute hydrochloric acid, caused hydrolysis of the ester group as well as the Smiles rearrangement, giving 4-(*N*-ethyl-2-hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic acid (**21**). The ring closure of **21** to **22** was smoothly effected in 73% yield by treatment of the acid **21** with boiling acetic anhydride (Chart VI). In agreement with the lactone structure, the ir spectrum of **22** showed its carbonyl absorption band at 5.76 μ. The isomeric 6-ethyl-2-phenylpyrimido[4,5-*b*][1,5]benzoxazepin-5(6*H*)-one would be expected to show its carbonyl absorption band at approximately 6.0 μ in view of the fact that in the closely related 6-(3-dimethylaminopropyl)-2-methylpyrimido[4,5-*b*][1,5]benzothiazepin-5(6*H*)one the carbonyl absorption band appears at 6.02 μ (3). As expected, the nmr spectrum of **22** did not manifest the unusual downfield shift of one of the phenyl protons that was observed in the case of **16a**, but exhibited the disubstituted phenyl ring proton signals at δ 7.27 ppm as an aromatic singlet.

Examination of the high resolution mass spectrum of **16a** in comparison with that of **22** provided further evidence in support of the structure **16a**. Upon radiation with a high energy electron beam, **16a** showed the base peak at m/e 289, which resulted from M^+ (m/e 331) with loss of C_2H_2O. The ion with m/e 289 constituted also a major peak in the spectrum of **22**. In this case, a fragmentation of C_2H_4 from M^+ (m/e 317) resulted in the generation of a m/e 289 ion. In both spectra, there were major peaks due to ions with m/e 261, 245, which were derived from the m/e 289 species with loss of fragments, CO and CO_2, respectively, (Chart VII).

A possible reaction sequence for the formation of **16a-c** from the reaction of **15a-c** and acetic anhydride may be formulated in the following equation (Chart VIII). An acetylation on the phenolic hydroxide group takes place initially to give an isolable intermediate **23**, which is followed by acetylation on the carboxylic acid group to form the mixed anhydride **24**. An intramolecular

Chart VII

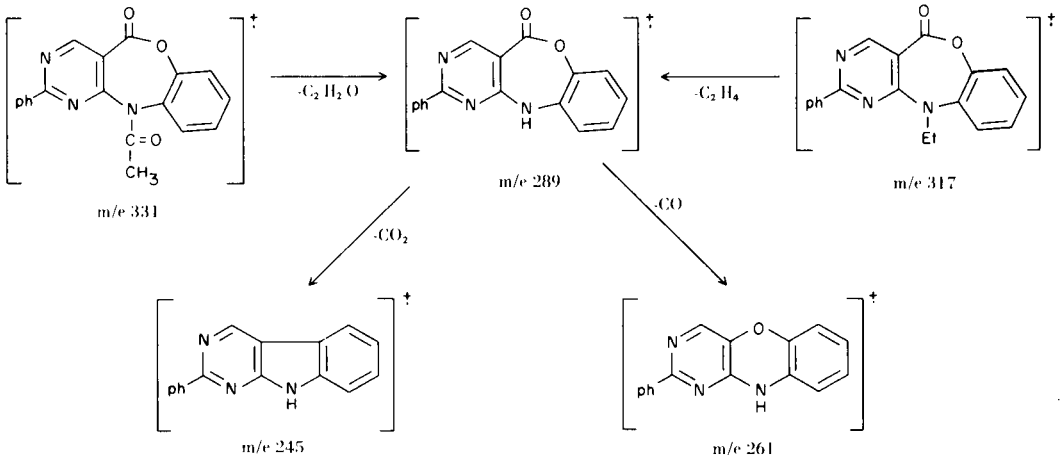
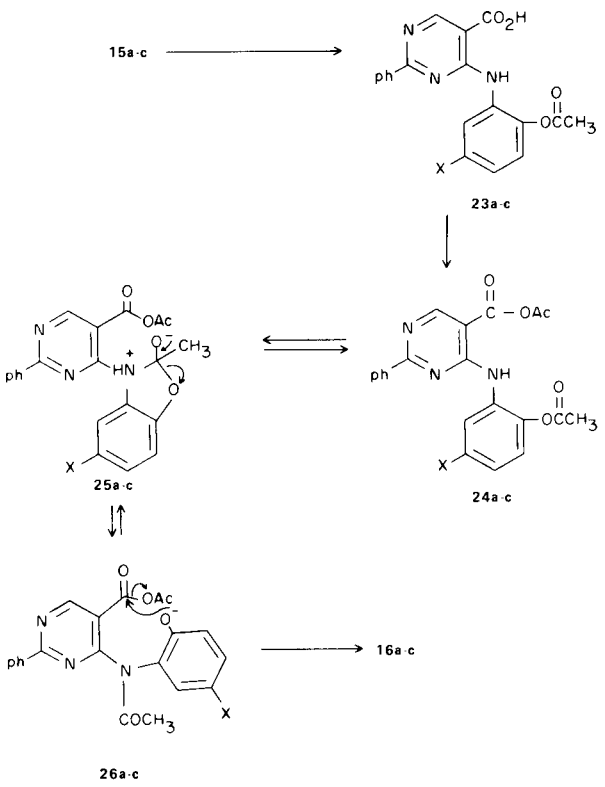
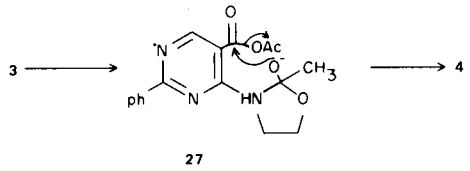


Chart VIII



nucleophilic attack on the phenoxyacetate carbonyl group by the C_4-amino nucleophile generates **25**. Such an intermediate had been postulated by Amundsen and Ambrosio for the process of O → N migration of acyl group in *o*-aminophenyl esters (8). Cleavage of the C-O bond of the oxazole ring in **25** affords the *N*-acetyl derivative **26**, which then undergoes cyclization by an intramolecular nucleophilic displacement of acetate ion by the newly generated phenoxide ion to give the final product **16a-c**. In this regard, it is interesting to note that structurally related **3**, in which the amino and the hydroxy groups are connected by an ethylene linkage, is known to cyclize differently to give **4** under comparable conditions (1).

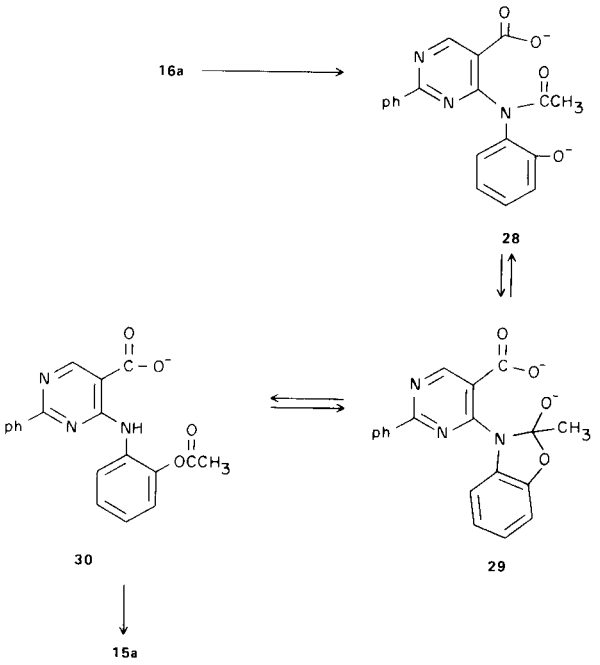
In this reaction, **27** was suggested (1) as an intermediate for the formation of **4**. Apparently, in the case of **27**, an intramolecular nucleophilic attack by the newly generated nucleophile on the carbonyl group of the



anhydride portion of the molecule precedes the cleavage of the annular C-O bond. The preferred cleavage of the annular C-O bond in the case of **25** may be attributed to the greater resonance stability of the phenoxide ion. When the length of heating time is shortened in the reaction of **15b** with acetic anhydride **23b** was isolated.

Treatment of **16a** with aqueous sodium hydroxide solution under refluxing conditions and subsequent acidification regenerated the starting acid **15a**. The hydrolysis appears to proceed with an initial cleavage of the lactone linkage to give an intermediate such as **28** which then isomerizes to **30** *via* the migration of the acetyl group from N → O as shown in Chart IX.

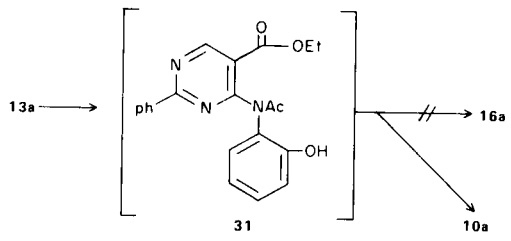
Chart IX



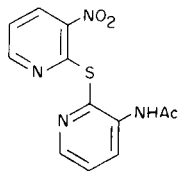
Hydrolysis of the acetate portion of **30** affords **15a**. In fact, when **16a** was hydrolyzed under carefully controlled conditions, **30** was isolated as a carboxylic acid (**23a**), which was readily converted into **15a** under conditions similar to those used for the hydrolysis. Treatment of **23b** with ethyl chloroformate afforded the corresponding ethyl ester (**10b**), which is identical with the product obtained from **8b** with acetic anhydride.

Finally, hoping to establish an alternative synthetic route to **16a**, **13a** was heated in pyridine under refluxing conditions. It would not be too unreasonable to expect that under the Smiles rearrangement conditions **13a** would yield the intermediate **31** which would then undergo a cyclization *via* an intramolecular displacement reaction with the loss of ethanol to form **16a** (Chart X).

Chart X



In fact, it was reported by Rodig, *et al.* that 3-acetamido-3′-nitro-2,2′-dipyridyl sulfide (**32**) rearranged to *N*-acetyl-2-mercapto-3′-nitro-3,2′-dipyridylamine (**33**) by treatment with potassium hydroxide in ethanol at 0° (9). However, heating of **13a** with pyridine under refluxing conditions



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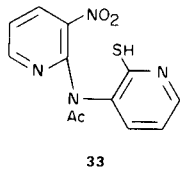

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failed to give the desired product, but instead afforded **10a** in quantitative yield. Apparently the migration reaction of the acetyl group from N → O in **31** occurs first, thus preventing the formation of the lactone ring.

EXPERIMENTAL

Melting points were taken in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Infrared spectra were obtained in potassium bromide pellets using a Perkin-Elmer 21 spectrophotometer, and ultraviolet absorption spectra were obtained with a Perkin-Elmer Model 450 uv-visible NIR spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal reference. Mass spectra were obtained with an Associated Electrical Industries MS-9 high resolution mass spectrometer. Elemental analyses were performed by the Analytical Section of these Laboratories.

4-(2-Hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**8a**).

From 4-Chloro-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**7**).

To an ethanolic solution containing 2.2 g. of 2-hydroxyaniline and 0.46 g. of sodium as sodium ethoxide in 45 ml. of absolute ethanol was added 5.3 g. of **7**. The resulting mixture was heated under reflux for 1 hour. Chilling of the reaction mixture in ice caused separation of a precipitate which was collected on a filter, giving 4.5 g. (67%) of product, m.p. 170-173°. Recrystallization from absolute ethanol afforded an analytical sample, m.p. 178.5-181°; ir 3.43, 3.50 (NH, OH), and 5.91 μ (C=O).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found : C, 68.33; H, 4.81; N, 12.70.

From 4-(2-Nitrophenoxy)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**9**).

A solution of 2.0 g. of **9** in 200 ml. of absolute ethanol was hydrogenated at 50° in the presence of 0.5 g. of 10% palladium on charcoal using a low pressure hydrogenator. It took *ca.* 75 minutes. After removing the catalyst by filtration, the ethanolic solution was concentrated under reduced pressure to *ca.* 60 ml., and chilled in ice. The precipitate which thus separated was collected on a filter and recrystallized from absolute ethanol, giving 1.8 g. (93%) of product (m.p. 178.5-181°) which is identical with the product from **7** by mixture m.p. and ir spectra comparison.

From 4-(2-Aminophenoxy)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**12a**) in Ethanol.

A solution of 1.0 g. of **12a** in 30 ml. of absolute ethanol was heated on a steam bath for 1 hour, then chilled in ice. The precipitate which thus separated was collected on a filter, giving a product, m.p. 178-181° which is identical with the authentic sample prepared from **7**.

From **12a**, Thermally.

A test tube containing 0.5 g. of **12a** was immersed in an oil bath maintaining the temperature of 180°, and kept for 15 minutes. The solid material thus obtained was recrystallized from absolute ethanol, giving **8a**, m.p. 178-181°. A mixture m.p. with the authentic sample prepared from **7** showed no depression.

4-(5-Chloro-2-hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**8b**). From **7**.

To a solution containing 1.2 g. of sodium (as sodium ethoxide) and 7.0 g. of 2-amino-4-chlorophenol in 300 ml. of absolute ethanol was added 13.0 g. of **7**. The resulting mixture was heated under reflux for 2 hours. Chilling of the reaction mixture in ice caused separation of a precipitate, which was collected on a filter and washed with ethanol several times then with water giving 13.6 g. (74%) of product, m.p. 247-251°. The analytical sample (m.p. 251-253°) was obtained by recrystallization from DMF; ir 5.92 μ (C=O).

Anal. Calcd. for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36; Cl, 9.59. Found: C, 61.38; H, 4.49; N, 11.56; Cl, 9.30.

From 4-(2-Amino-5-chlorophenoxy)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**12b**).

A test tube containing 1.0 g. of **12b** was immersed in an oil bath maintained at a temperature of 180°. The temperature was raised to 210° and kept for 20 minutes. The solid material thus obtained was recrystallized from DMF, giving 1.0 g. (100%) of product (m.p. 251-253°) which is identical with the sample prepared from **7** when tested by mixture m.p.

4-(2-Hydroxy-5-nitroanilino)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**8c**).

To a methanol solution prepared by dissolving 1.2 g. of sodium in 70 ml. of absolute methanol was added, with stirring, 7.5 g. of 2-amino-4-nitrophenol. The stirring was continued for 20 minutes. Removal of the methanol from the resulting solution *in vacuo* afforded the sodium salt of the 2-amino-4-nitrophenol which was then dissolved in 50 ml. of DMF. To the resulting solution was added with stirring 13.0 g. of **7**. The stirring was continued for 0.5 hour at room temperature, then heated on a steam bath for 15 minutes. Pouring of the reaction mixture into a large amount of cold water caused separation of a precipitate which was collected on a filter and washed with water several times. Recrystallization of the filter residue from DMF afforded 10 g. (53%) of product, m.p. 277-279° dec. Another recrystallization from DMF afforded an analytical sample, m.p. 285-286° dec.; ir 5.95 μ (C=O).

Anal. Calcd. for $C_{19}H_{16}N_4O_5$: C, 59.99; H, 4.24; N, 14.73. Found: C, 59.87; H, 4.32; N, 14.50.

4-(2-Nitrophenoxy)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**9**).

To a methanol solution prepared by dissolving 2.3 g. of sodium in 70 ml. of absolute ethanol was added 14 g. of 2-nitrophenol whereby a dark red color developed. After stirring the resulting mixture for 10 minutes, the methanol was removed under reduced pressure to give a solid residue. The residue was dissolved in 70 ml. of DMF. To the DMF solution was added 26.3 g. of **7** with stirring, and the mixture was heated under reflux for 1 hour. The hot reaction mixture was filtered, and the filtrate was chilled in ice to cause a separation of a precipitate. The precipitate was collected on a filter, giving 29 g. (80%) of product, m.p. 150-154°. Recrystallization from absolute ethanol afforded an analytical sample, m.p. 151-154°; ir 5.81 μ (C=O).

Anal. Calcd. for $C_{19}H_{15}N_3O_5$: C, 62.46; H, 4.14; N, 11.50. Found: C, 62.33; H, 4.09; N, 11.36.

4-(2-Aminophenoxy)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**12a**).

Three and three-tenths grams of 2-aminophenol was added to a methanol solution obtained by dissolving 0.7 g. of sodium in 50 ml. of absolute methanol. After stirring the resulting solution for a few minutes, the methanol was removed *in vacuo* to give sodium salt of the 2-aminophenol. The salt was dissolved in 70 ml. of DMF. To the solution was added 7.9 g. of **7** in small portions with cooling in ice. Stirring and cooling were continued for an additional 15 minutes. Pouring of the reaction mixture into a large amount of ice water caused separation of an oil which solidified on scratching. The solid material was collected on a filter. Fractional recrystallization from ether with cooling in dry ice-2-propanol caused separation of two fractions. Recrystallization of the more soluble fraction from ether afforded a product which melted at 102°, solidified, then remelted at 173-175°; ir 2.95, 3.05 (NH_2), and 5.85 μ (C=O).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.05; H, 5.11; N, 12.24.

4-(2-Amino-5-chlorophenoxy)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**12b**).

This compound was prepared in a similar fashion to **12a** from 2-amino-4-chlorophenol and **7** and recrystallized from absolute ethanol; m.p. 144-146° (solidified and remelted at 246-250°); ir 3.00, 3.05 (NH_2), and 5.83 μ (C=O).

Anal. Calcd. for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36; Cl, 9.59. Found: C, 61.78; H, 4.41; N, 11.34; Cl, 9.45.

4-(2-Hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester Acetate (**10a**). From **8a**.

To a solution obtained by dissolving 1.0 g. of **8a** in 15 ml. of pyridine was added dropwise 0.4 g. of acetic anhydride. The resulting mixture was heated on a steam bath for 1 hour. The pyridine was removed under reduced pressure to give a crystalline residue. Recrystallization from cyclohexane afforded 0.5 g. (45%) of an analytical sample, m.p. 152-154°; ir 5.63 (-OAc), and 5.93 μ (CO_2Et).

Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.75; H, 5.32; N, 11.27.

From 4-(2-*N*-acetylaminophenoxy)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**13a**).

A mixture of **13a** (0.7 g.) and pyridine (25 ml.) was heated under reflux for 3 hours, then the excess pyridine was removed under reduced pressure to give an oil which crystallized on chilling, m.p. 140-142.5°, yield 0.7 g. (100%). The ir spectrum of this compound was identical with that of an authentic sample prepared from **8a**.

4-(5-Chloro-2-hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester Acetate (**10b**). From **8b**.

To a pyridine solution containing 3.7 g. of **8b** was added dropwise 2.0 g. of acetic anhydride. The resulting mixture was heated under reflux for 0.5 hour. Chilling of the reaction mixture in ice caused separation of a precipitate which was collected on a filter and washed with ethanol, giving 3.2 g. (77.5%) of product, m.p. 159-160°. Recrystallization from pyridine raised the m.p. to 160-162°; ir 5.65 (OAc) and 5.90 μ (CO_2Et).

Anal. Calcd. for $C_{21}H_{18}ClN_3O_4$: C, 61.24; H, 4.64; N, 10.18; Cl, 8.59. Found: C, 61.17; H, 4.74; N, 10.37; Cl, 8.84.

From 4-(5-chloro-2-hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic Acid Acetate (**23b**).

A mixture of **23b** and an excess of ethyl chloroformate was heated under reflux overnight. Removal of the excess ethyl chloroformate under reduced pressure afforded a solid residue which was recrystallized from aniline, m.p. 154-155°. The ir spectrum of this compound was identical with that of **10b** prepared from **8b**.

4-(2-*N*-Acetylaminophenoxy)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**13a**).

To a cold pyridine solution obtained by dissolving 2.0 g. of **12a** in 20 ml. of pyridine was added dropwise 1.0 g. of acetic anhydride with stirring and chilling in ice. The resulting mixture was stirred under chilling in ice for 1 hour, whereby a precipitate separated. The precipitate was collected on a filter and washed with water to give 1.7 g. (76%) of product, m.p. 140°. Recrystallization from absolute ethanol afforded an analytical sample, m.p. 138-140°; ir 3.00 (NH), 5.85 (-CO_2Et), and 6.20 μ (-$NHCOCH_3$).

Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.14. Found : C, 66.45; H, 5.00; N, 11.20.

4-(2-Hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic Acid (**15a**). From **8a**.

A mixture of **8a** (3.2 g.), 40% aqueous potassium hydroxide solution (10 ml.) and ethanol (20 ml.) was heated under reflux for 2.5 hours. Chilling of the reaction mixture in ice caused precipitation of the sodium salt of the product which was collected on a sintered glass filter. The filter residue was dissolved in hot water, and acidified with dilute hydrochloric acid which caused separation of a product. This was collected on a filter and washed with water. Purification of the product was made by dissolving it in 0.5 *N* aqueous sodium hydroxide solution and reprecipitation by acidification with dilute hydrochloric acid, giving 2.0 g. (69%) of product, m.p. 285-289° dec.; ir 6.05 μ (C=O).

Anal. Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.68. Found: C, 66.51; H, 4.15; N, 13.48.

From **12a**.

A mixture of **12a** (0.3 g.), 15% aqueous sodium hydroxide solution (20 ml.) and ethanol (3 ml.) was heated under reflux for 2 hours. Acidification of the reaction mixture with dilute hydrochloric acid to *p*H 2 caused separation of a precipitate which was collected on a filter and washed with water several times, giving 0.28 g. (95%) of product, m.p. 290-292° dec. A mixture m.p. with a sample prepared from **8a** was not depressed.

4-(5-Chloro-2-hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic Acid (**15b**).

A mixture of **8b** (10 g.), 20% aqueous sodium hydroxide solution (200 ml.) and ethanol (10 ml.) was heated under reflux for 20 minutes, then acidified with dilute hydrochloric acid. The precipitate thus separated was collected on a filter and washed with water several times, giving 9.2 g. (95%) of product, m.p. 295-297°. Purification by dissolving in dilute aqueous sodium hydroxide solution and reprecipitation by acidification raised the m.p. to 298-300° dec.; ir 6.04 μ (CO_2H).

Anal. Calcd. for $C_{17}H_{12}ClN_3O_3$: C, 59.76; H, 3.54; N, 12.30. Found: C, 59.59; H, 3.58; N, 12.44.

4-(2-Hydroxy-5-nitroanilino)-2-phenyl-5-pyrimidinecarboxylic Acid (**15c**).

This compound was prepared from **8c** by base hydrolysis in the same fashion as **15b**, m.p. 330° dec., ir 6.1.0 μ (C=O).

Anal. Calcd. for $C_{17}H_{12}N_4O_5 \cdot H_2O$: C, 55.13; H, 3.81. N, 15.13. Found: C, 55.24; H, 3.60; N, 14.88.

11-Acetyl-2-phenylpyrimido[5,4-*c*][1,5]benzoxazepin-5(11*H*)one (**16a**).

A mixture of **15a** (1.0 g.) and acetic anhydride (25 ml.) was heated to reflux. A clear solution was obtained in 15 minutes. The refluxing was continued for an additional 45 minutes, and the excess acetic anhydride was then removed under reduced pressure, giving an oil which solidified on chilling. The solid material was collected on a filter and washed with acetic anhydride, giving 0.55 g. (51%) of product, m.p. 219-225°. Recrystallization from acetic anhydride afforded an analytical sample, m.p. 221-223.5°; ir 5.72 (lactone C=O) and 6.20 μ (amide C=O); uv λ max (95% ethanol) 278 mμ (broad, ϵ 27,000); mass spectrum m/e (rel. intensity) 331 (41), 289 (100), 261 (18), 245 (1.4), 186 (7), 158 (10), 155 (5), 130 (7), 104 (18), and 103 (25).

Anal. Calcd. for $C_{19}H_{13}N_3O_3$: C, 68.87; H, 3.96; N, 12.68. Found: C, 69.08; H, 3.70; N, 12.61.

Hydrolysis of **16a** with 10% aqueous sodium hydroxide solution and subsequent acidification with dilute hydrochloric acid afforded a product, m.p. 298° dec., identical with **15a** prepared from **8a** (ir and mixture m.p.).

11-Acetyl-9-chloro-2-phenylpyrimido[5,4-*c*][1,5]benzoxazepin-5(11*H*)one (**16b**).

A mixture of **15b** (4.5 g.) and acetic anhydride (100 ml.) was heated under gentle reflux for 2.5 hours, treated with charcoal, and filtered. Chilling of the filtrate caused separation of a precipitate which was collected on a filter and dried over potassium hydroxide *in vacuo* at 100°, giving 1.5 g. (31%) of product, 223-228°. Recrystallization from acetic anhydride raised the m.p. to 243-246°; ir 5.68 (C=O) and 6.20 μ (C=O).

Anal. Calcd. for $C_{19}H_{12}ClN_3O_3$: C, 62.39; H, 3.31; N, 11.49. Found: C, 62.73; H, 3.20; N, 11.52.

11-Acetyl-9-nitro-2-phenylpyrimido[5,4-*c*][1,5]benzoxazepin-5(11*H*)one (**16c**).

A mixture of **15c** (1.1 g.) and acetic anhydride (25 ml.) was heated under reflux for 1.5 hours. Chilling of the reaction mixture caused separation of a precipitate which was collected on a filter. Repeated recrystallization from acetic anhydride afforded 0.7 (64%) of an analytical sample, m.p. 284-285°; ir 5.68 μ (C=O).

Anal. Calcd. for $C_{19}H_{12}N_4O_5$: C, 60.64; H, 3.21; N, 14.89. Found: C, 60.49; H, 3.34; N, 15.06.

2-*N*-Acetylaminophenol Acetate (**18**).

To a pyridine solution (40 ml.) containing 9.6 g. of *o*-aminophenol was added slowly 19.8 g. of acetic anhydride, whereby an exothermic reaction took place. When the temperature had subsided, the reaction mixture was heated on a steam bath for 0.5 hour, then chilled in a freezer. The precipitate thus separated was collected on a filter and washed with water, giving 12.4 g. (78.5%) of product, m.p. 122-125°. Lit. m.p. (10) 124.5°.

2-*N*-Ethylaminophenol (**19**).

To a suspension of lithium aluminum hydride (2.48 g.) in 35 ml. of tetrahydrofuran was added dropwise 8.4 g. of **18** dissolved in 95 ml. of tetrahydrofuran. The resulting mixture was heated under reflux for 2 hours, then treated with 2.5 ml. of water 2.5 ml. of 15% aqueous sodium hydroxide solution, and

7.5 ml. of water successively. After removing the inorganic salt by filtration, the tetrahydrofuran was evaporated under reduced pressure giving an oil; ir 2.92 (NH,OH) and 6.00 μ (C=O). This oil was used directly in the subsequent reaction.

4-(2-Ethylaminophenoxy)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (**20**).

To an ethanolic solution containing 2-*N*-ethylaminophenol in 70 ml. of absolute ethanol was added in small portions 15 g. of **7**, and the resulting mixture was heated under reflux for 45 minutes. Addition of a large amount of water to the reaction mixture caused separation of a precipitate which was collected on a filter and washed with water, then with ether, giving 23 g. (quantitative) of product, m.p. 165-167°; ir 5.83 μ (C=O).

Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.28; H, 5.94; N, 11.57.

4-(2-Hydroxy-*N*-ethylanilino)-2-phenyl-5-pyrimidinecarboxylic Acid (**21**).

A mixture of **20** (7.0 g.), 15% aqueous sodium hydroxide solution (50 ml.), and ethanol (20 ml.) was refluxed for 3 hours, then acidified with dilute hydrochloric acid to *p*H ~ 2. The precipitate was collected on a filter and washed with ethanol, then with water, giving 6.1 g. (90%) of product. Recrystallization from ethanol-water afforded a sample which melted at 150-154°. solidified and remelted at 190°; ir 3.7-4.0 (broad, C-O*H*) and 5.90 μ (weak, C=O).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.50; H, 5.03; N, 12.39.

11-Ethyl-2-phenylpyrimido[5,4-*c*][1,5]benzoxazepin-5(11*H*)one (**22**).

A mixture of **21** (4.0 g.) and acetic anhydride (100 ml.) was refluxed for 3 hours. Removal of the excess acetic anhydride under reduced pressure afforded an oil which solidified on standing, giving 3.1 g. (82%) of product, m.p. 130-133°. Recrystallization from absolute ethanol raised the m.p. to 133-134°; ir 5.76 μ (C=O), uv λ max (95% ethanol) 284 mμ (ϵ 34,700); mass spectrum (rel. intensity) 317 (100), 302 (28), 289 (43), 274 (10), 258 (9), 245 (12), 183 (7), 134 (21), and 103 (25).

Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.90; H, 4.91; N, 13.62.

4-(2-Hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic Acid Acetate (**23a**).

A mixture of **16a** (0.5 g.), ethanol (17 ml.) and concentrated hydrochloric acid (4 drops) was stirred at room temperature for 20 minutes, then chilled in ice. The precipitate was collected on a filter and washed with ethanol, then with water. The crude product was recrystallized from dimethylformamide, m.p. 232-234° dec.; ir 4.15 (broad), 5.63 (-OAc), and 5.98 μ (COOH).

Anal. Calcd. for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 64.93; H, 4.60; N, 12.28.

4-(5-Chloro-2-hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic Acid Acetate (**23b**).

A mixture of 3.6 g. of **15b** and 65 ml. of acetic anhydride was heated under reflux for 1.5 hours and filtered hot after being treated with charcoal. Chilling of the filtrate in ice caused separation of a precipitate which was collected on a filter and dried over potassium hydroxide *in vacuo* at 180°, giving 1.8 g. (44%) of product. The crude product was recrystallized from dimethylformamide, m.p. 279-281° dec.; ir 3.95 (broad), 5.65 (-OAc), and 6.00 μ (COOH).

Anal. Calcd. for $C_{19}H_{14}ClN_3O_4$: C, 59.46; H, 3.94; N, 10.95. Found: C, 59.31; H, 3.81; N, 10.98.

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