Synthesis of Pyrido[1,2-*a*]pyrimido[4,5-*d*]pyrimidin-5-ones. Cyclization Reaction of 4-[(3-Hydroxy-2-pyridyl)amino]-2-phenyl-5-pyrimidinecarboxylic Acid with Acetic Anhydride.

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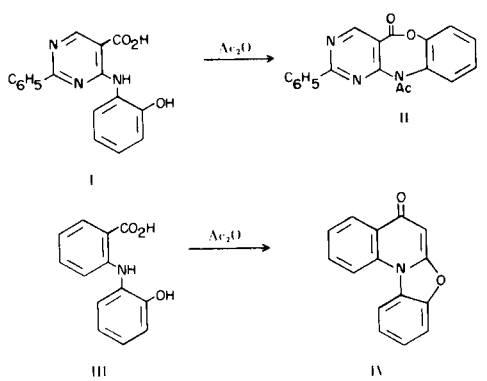
Received December 6, 1974

Treatment of 4-[(3-hydroxy-2-pyridyl)amino]-2-phenyl-5-pyrimidinecarboxylic acid (X) with acetic anhydride under refluxing conditions afforded 10-hydroxy-2-phenyl-5*H*-pyrido[1,2-*a*]-pyrimido[4,5-*d*]pyrimidin-5-one acetate (IX). The intermediate X was prepared from 4-chloro-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (V). The reaction of V with the sodium salt of 2-amino-3-hydroxypyridine at room temperature gave 4-(2-amino-3-pyridyloxy)-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (VI). Treatment of VI with a hot aqueous sodium hydroxide solution and subsequent acidification gave X. Involvement of 4-[(3-hydroxy-2-pyridyl)amino]-2-phenyl-5-pyrimidinecarobxylic acid ethyl ester (VIII) (Smiles rearrangement product) as an intermediate in the above alkaline hydrolysis reaction of VI to X was demonstrated by the isolation of VIII and its subsequent conversion into X under alkaline hydrolysis conditions. Acetylation of VIII with acetic anhydride in pyridine solution gave 4-[(3-hydroxy-2-pyridyl)amino]-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester acetate (XI), which afforded IX on fusion at 220°. This alternative synthesis of IX from XI supported the structural assignment of IX. Fusion of VI gave 10-hydroxy-2-phenyl-5*H*-pyrido[1,2-*a*]pyrimido[4,5-*d*]pyrimidin-5-one (VII). The latter was also obtained when VIII was fused at 210°. Acetylation of VII with acetic anhydride afforded IX.

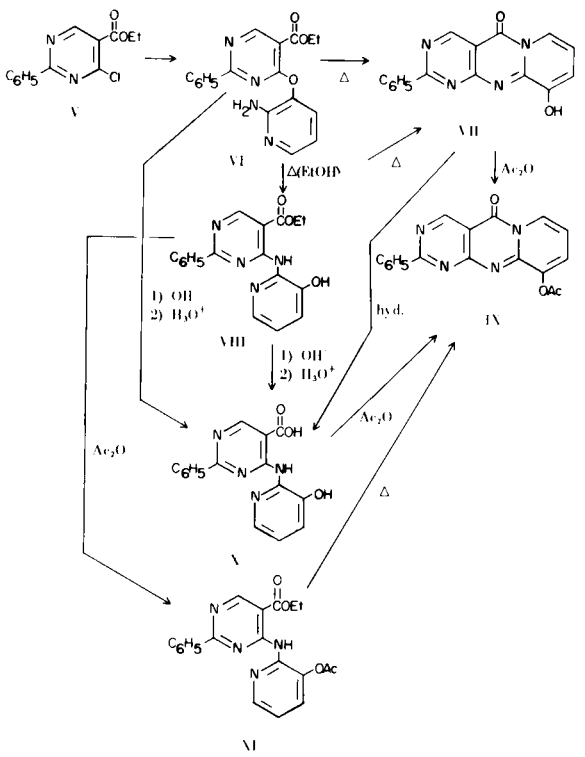
Previously, we reported on the cyclization reaction of 4-(2-hydroxyanilino)-2-phenyl-5-pyrimidinecarboxylic acid (I) to 11-acetyl-2-phenylpyrimido[5,4-*c*][1,5]benzoxazepin-5(11*H*)one (II) by treatment with refluxing acetic anhydride (1). Under similar conditions, however, *N*-(2-hydroxyphenyl)anthranilic acid (III) cyclized differently giving 5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (IV) (Chart I) (2). We now report on the cyclization reaction of 4-[(3-hydroxy-2-pyridyl)amino]-2-phenyl-5-pyrimidinecarboxylic acid (X).

(Chart I)



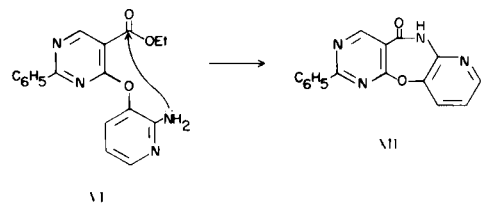
Treatment of 4-chloro-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (V) with the sodium salt of 2-amino-3-hydroxypyridine in ethanol under controlled conditions gave 4-(2-amino-3-pyridyloxy)-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (VI) (Chart II). Heating an ethanol solution of VI caused a Smiles type of rearrangement to occur, giving 4-[(3-hydroxy-2-pyridyl)amino]-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (VIII). Whereas the infrared spectrum of VI showed a carbonyl absorption band at 5.81 μ, the rearrangement product VIII exhibited a band at 5.93 μ. The observed shift of the positions of the infrared carbonyl absorption bands accompanying the rearrangement was anticipated, since the carbonyl group of VIII was expected to be involved in an intramolecular hydrogen bond formation with the *o*-amino proton. Treatment of VIII with an aqueous sodium hydroxide solution followed by acidification afforded the corresponding acid X. The acid X was also obtainable directly from VI under similar alkaline hydrolysis conditions. In the latter approach, apparently, hydrolysis of the ester group was accompanied by a Smiles type rearrangement under the reaction conditions. It is well known that the Smiles rearrangement is apt to take place in an alkaline medium (3).

(Chart II)

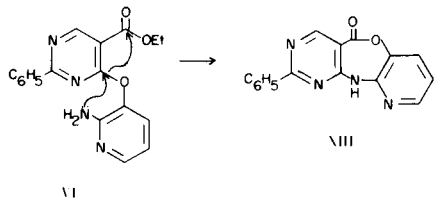


When the acid X was heated with a large amount of acetic anhydride under refluxing conditions, a cyclization reaction took place to form the lactam IX. The assigned structure was indicated by the presence of two carbonyl absorption bands in its infrared spectrum: 5.65 μ for the acetoxy carbonyl and 5.85 μ for the lactam carbonyl. The following alternative synthesis of IX presented further support for the assigned structure. Controlled acetylation of VIII with acetic anhydride in pyridine gave the *O*-acetylated derivative XI, as shown by its new ir band at 5.62 μ. Thermal cyclization of the acetate XI, brought about by heating neat at 220° for 15 minutes, gave a compound which is identical with IX obtained from X by acetic anhydride cyclization.

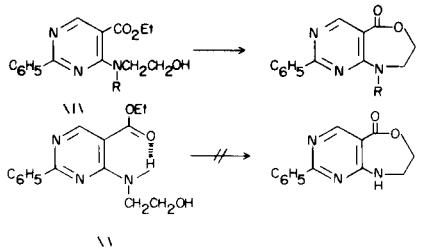
It was thought to be of interest to investigate the mode of cyclization of VI under thermal conditions. If a cyclization reaction precedes the Smiles rearrangement, then the formation of a 7-membered ring lactam such as XII is expected. On the other hand, if the Smiles rearrangement



and lactone formation take place simultaneously in a concerted fashion, the formation of a 7-membered lactone such as XIII may occur. Recently, it was reported that



while 4-[(2-hydroxyethyl)alkylamino]-2-phenyl-5-pyrimidinecarboxylic acid ethyl esters (XIV) cyclize readily to form 7-membered lactones (4,5), the corresponding *N*-unsubstituted derivatives such as 4-(2-hydroxyethylamino)-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (XV) resists cyclization under various reaction conditions (5,6). The failure of the cyclization reaction in the case of XV was thought to be due to an unfavorable configuration of the hydroxy group for a nucleophilic attack on the ester carbonyl which is involved in an intramolecular hydrogen bonding with the amino proton (6). Furthermore,



should the Smiles rearrangement proceed with formation of a stable intermediate such as VIII, then the final product of the thermal ring closure reaction would be a thermodynamically stable 6-membered lactam such as VII.

The thermal cyclization reaction was carried out by heating VI neat in an oil bath maintaining the temperature at 210° for 20 minutes. The product thus obtained melted at 261-263°, and showed bands at 5.85 (C=O) and 3.10 (OH) μ in its infrared spectrum. The uv spectrum of this compound closely resembled that of IX, showing absorption peaks at 284 (2.27×10^4) and 365 (0.71×10^4) mμ. On the basis of the above spectral data and the combustion analytical result, 10-hydroxy-2-phenyl-5*H*-pyrido[1,2-*a*]-pyrimido[4,5-*d*]pyrimidin-5-one (VII) was assigned for the cyclization product. In support of the structural assignment, when VII was allowed to react with refluxing acetic anhydride, there was obtained an *O*-acetylated derivative which is identical with IX prepared from XI. The involvement of the Smiles rearrangement product VIII in the above thermal ring closure reaction was demonstrated by the transformation of VIII to VII under conditions similar to those used for the preparation of VII from VI. Treatment of VII with boiling aqueous sodium hydroxide solu-

tion and subsequent acidification gave a ring-cleaved product (X).

Compounds VII and IX showed CNS depressant activity when tested in mice using a previously described procedure (7).

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. Uv absorption spectra were obtained with a Perkin-Elmer 450 uv-visible NIR spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal reference. Combustion elemental analyses were performed by the Analytical Section of these Laboratories. The reported yields may be improved under optimal reaction conditions.

4-(2-Amino-3-pyridyloxy)-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (VI).

To a freshly prepared sodium ethoxide-ethanol solution obtained by dissolving 1.1 g. of sodium in 170 ml. of absolute ethanol was added 5.6 g. of 2-amino-3-hydroxypyridine. The resulting solution was stirred at room temperature for 10 minutes. Thirteen grams of 4-chloro-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester was added. The resulting mixture was warmed on a steam bath for 30 minutes, then chilled in ice. The precipitate thus separated was collected on a filter and washed with ethanol, then with water several times. The product amounted to 13 g. and melted at 151-153°. Recrystallization of the product from ethanol gave an analytical sample, m.p. 152-154°; ir: μ 2.97, 3.05 (NH_2) and 5.81 (C=O); uv λ max (95% ethanol): 286 mμ (ϵ, 28,200); nmr (deuteriochloroform): δ 1.33 (t, 3H, CH_2CH_3), 4.20 (q, 2H, CH_2CH_3), and 5.13 (s, 2H, NH_2).

Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.27; H, 4.80; N, 16.66. Found: C, 63.93; H, 4.85; N, 16.88.

4-[(3-Hydroxy-2-pyridyl)amino]-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (VIII).

A mixture of VI (1.5 g.) and absolute ethanol (100 ml.) was heated under reflux for 6 hours. The hot solution was treated with activated charcoal and filtered. Chilling of the filtrate in ice caused separation of a precipitate which was collected on a filter and recrystallized from ethanol, giving 0.5 g. of a yellow crystalline product, m.p. 179-181°; ir: μ 2.95, 3.25 (NH, OH) and 5.93 (C=O); uv λ max (95% ethanol): 280 mμ (ϵ, 17,770); nmr (deuteriochloroform): δ 1.43 (t, 3H, CH_2CH_3), 4.39 (q, 2H, CH_2CH_3), 10.41 (s, 1H, NH or OH), and 11.51 (s, 1H, NH or OH).

Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.27; H, 4.80; N, 16.66. Found: C, 64.45; H, 4.75; N, 16.45.

4-[(3-Hydroxy-2-pyridyl)amino]-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester Acetate (XI).

To a pyridine solution obtained by dissolving 3.3 g. of VIII in 50 ml. of pyridine was added dropwise 1.2 g. of acetic anhydride. The resulting mixture was heated to reflux for 20 minutes. Evaporation of pyridine on a rotary evaporator under reduced pressure gave an oily residue which solidified on standing. The solid was triturated with water, then recrystallized from ethanol giving 3.5 g. of product, m.p. 99-101.5°; ir: μ 3.08 (NH), 5.62 (-O-C(=O)Me) and 5.89 (CO_2Et).

Anal. Calcd. for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.80; N, 14.81. Found: C, 63.57; H, 4.95; N, 14.70.

4-[(3-Hydroxy-2-pyridyl)amino]-2-phenyl-5-pyrimidinecarboxylic Acid (X).

A. From VI.

A conventional alkaline hydrolysis of VI with 15% aqueous sodium hydroxide solution and subsequent acidification gave X in a near quantitative yield. Recrystallization from DMF gave an analytical sample, m.p. 246-249° dec; ir: μ 3.00 (broad, OH), 3.90 and 6.15 (CO_2^-).

Anal. Calcd. for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.18. Found: C, 61.98; H, 4.08; N, 18.55.

B. From VII.

A conventional alkaline hydrolysis of VIII followed by acidification also gave X, m.p. 243-245°, which is identical with that prepared from VI.

C. From VII.

A mixture of VII (3.2 g.), 20% aqueous sodium hydroxide solution (30 ml.) and ethanol (15 ml.) was heated under reflux for 20 minutes. The solution was then neutralized first with concentrated hydrochloric acid, then made acidic with dilute hydrochloric acid. The precipitate thus separated was collected on a filter and washed with water several times, giving X which is identical with that prepared from VI by method A.

10-Hydroxy-2-phenyl-5*H*-pyrido[1,2-*a*]pyrimido[4,5-*d*]pyrimidin-5-one (VII).

A. From VI.

A test tube containing 1.0 g. of VI was immersed in an oil bath. The oil bath was heated to 210° and maintained at the temperature for 20 minutes. The solid cake thus obtained was recrystallized from DMF, giving 0.9 g. (100%) of product, m.p. 261-263°; ir: μ 3.90 (broad, OH), and 5.87 (C=O); uv λ max (95% ethanol): 284 (ϵ, 22,700), 365 mμ (ϵ, 7,000).

Anal. Calcd. for $C_{16}H_{10}N_4O_2$: C, 66.20; H, 3.47; N, 19.30. Found: C, 66.39; H, 3.30; N, 19.42.

B. From VIII.

Fusion of VIII in an oil bath maintaining a temperature of 200 ± 10° for 7 minutes gave a product which is identical with VII prepared from VI by method A. The identity was based on m.p. no depression of mixture m.p. with VIII prepared from VI, and comparison of ir spectra.

10-Hydroxy-2-phenyl-5*H*-pyrido[1,2-*a*]pyrimido[4,5-*d*]pyrimidin-5-one Acetate (IX).

A. From VII.

A mixture of VII (1.8 g.) and acetic anhydride (60 ml.) was heated under reflux for 1.5 hours, then chilled in ice. The precipitate thus formed was collected on a filter, giving 2.0 g. (97%) of product, m.p. 305-308° dec; ir: μ 5.63 ($OCCH_3$) and 5.83 (C=O) uv λ max (95%, ethanol): 280 (shoulder, ϵ, 21,400), 302 (ϵ, 23,700), and 3.65 mμ (ϵ, 10,000).

Anal. Calcd. for $C_{18}H_{12}N_4O_3$: C, 65.05; H, 3.64; N, 16.86. Found: C, 64.88; H, 3.91; N, 16.50.

B. From X.

A mixture of X (2.6 g.) and acetic anhydride (30 ml.) was heated under reflux for 1.5 hours. Chilling of the mixture caused

separation of a precipitate which was collected on a filter and recrystallized from acetic anhydride, giving 1.2 g. (43%) of the product, m.p. 293° dec. The ir spectrum of this compound was identical with that of IX obtained from VII by method A.

Anal. Calcd. for $C_{18}H_{12}N_4O_3$: C, 65.05; H, 3.64; N, 16.86. Found: C, 64.87; H, 3.79; N, 16.50.

C. From XI.

Six tenths g. of XI was fused in a test tube at 220 ± 5° for 15 minutes. The solid cake was then recrystallized from DMF, giving a product with m.p. 293-296° dec. The mixture m.p. with IX prepared from VII was not depressed.

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