Synthesis of 5-Substituted-7-methoxy-2-phenylpyrimido[4,5-*b*]quinolines New Synthesis of Pyrimido[4,5-*b*]quinolines

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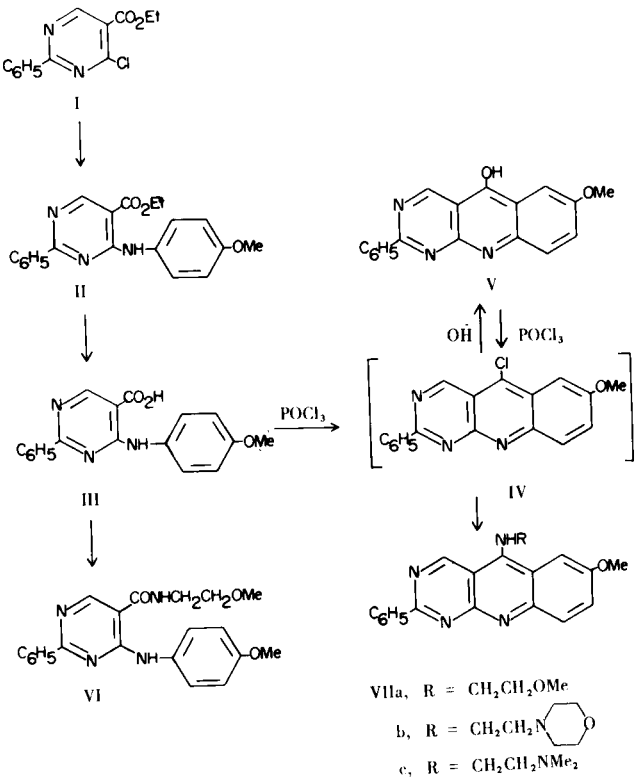
Although the first example of the pyrimido[4,5-*b*]-quinoline ring system was reported as early as 1901 (1), the ring system received little attention until the importance of its derivatives as a potential riboflavin antagonist was realized a couple of decades ago (2,3). Currently available synthetic routes to pyrimido[4,5-*b*]quinolines can be classified into two groups: (a) condensation of barbituric acid and related pyrimidine derivatives with *o*-aminobenzaldehydes (1,2,4,6), and (b) construction of fused pyrimidine nucleus from *o*-aminonitrile or *o*-aminocarboxamide of quinolines (7).

In continuing our work on the use of 5-carbethoxy-4-chloropyrimidines and related heterocyclic compounds as starting materials for the syntheses of fused pyrimidine heterocycles (8) with potential pharmacological interest, we have prepared 5-substituted-7-methoxy-2-phenylpyrimido[4,5-*b*]quinolines by a new approach. We believe that the new method exemplified in this report can be employed in the synthesis of a variety of pyrimido[4,5-*b*]-quinoline derivatives either by choosing appropriate starting materials, or by chemical manipulation of the ring closure product. Simplicity and high yield are the advantages of the present method over previous ones.

Treatment of 5-carbethoxy-4-chloro-2-phenylpyrimidine with *p*-anisidine in refluxing DMF in the presence of sodium carbonate afforded 4-*p*-anisidino-5-carbethoxy-2-phenylpyrimidine (II) in a quantitative yield. Alkaline hydrolysis of II followed by acidification gave the corresponding carboxylic acid, III. Cyclization of III was effected with excess phosphorus oxychloride under Magidson-Grigorowski conditions (5) giving an unstable deep red crystalline product. The latter compound was smoothly converted into 5-hydroxy-7-methoxy-2-phenylpyrimido[4,5-*b*]quinoline (V) by treatment with an aqueous solution of sodium carbonate. The assignment of the 5-hydroxy form V rather than its isomeric keto structure was based on the ir spectral data which showed a broad absorption band at 3.35 μ but was devoid of any absorption signals in the carbonyl region. Although the exact nature of the red product is not fully understood due to its instability, the chemical properties of the compound agree with the assigned structure, 5-chloro-7-methoxy-2-phenylpyrimido[4,5-*b*]quinoline (IV). Reversion of V to IV took place when V was heated with excess phosphorus oxychloride. Our interest in the biological evaluation of pyrimido[4,5-*b*]quinoline derivatives with pharmacophoric amines directed us to prepare the derivatives VIIa-c. The dechloroamination reactions for the preparation of VIIa-c were effected smoothly by the treatment of IV with the corresponding amines. The cyclization reaction of III to IV under the present conditions also gave the corresponding acid chloride as shown by the isolation of VI (see experimental section) after the treatment with 2-methoxyethylamine.

Scheme I



EXPERIMENTAL

Melting points were determined in capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were obtained in potassium bromide discs using a Perkin-Elmer spectrophotometer Model 21. Uv absorption spectra were obtained with a Perkin-Elmer spectrophotometer Model 450. Combustion elemental analyses were carried out by the Analytical Section of these laboratories.

4-*p*-Anisidino-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (II).

A mixture of 4-chloro-2-phenyl-5-pyrimidinecarboxylic acid ethyl ester (3.95 g.), *p*-anisidine (2.2 g.), sodium carbonate (1.9 g.) and DMF (50 ml.) was heated under reflux for 1.5 hours. After removing inorganic salt by filtration, the reaction mixture was poured into an equal amount of water whereby a precipitate separated. The precipitate was collected on a filter and washed with water giving 5.2 g. of product, m.p. 111-114°. Recrystallization from absolute ethanol improved the m.p. to 111-113.5°; ir 3.10 (NH) and 5.92 (C=O).

Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.79; H, 5.42; N, 11.70.

4-*p*-Anisidino-2-phenyl-5-pyrimidinecarboxylic Acid (III).

A mixture of II (2.5 g.) and 20% aqueous sodium hydroxide solution (20 ml.) was refluxed for 2 hours. After cooling to room temperature, the reaction mixture was acidified with dilute hydrochloric acid whereby a precipitate was formed. The precipitate was collected on a filter and recrystallized from DMF and water. The product melted at 268-270° with decomposition; ir: 3.25 (NH), and 4.25, 5.98 μ (CO_2H).

Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.38; H, 4.81; N, 12.81.

5-Chloro-7-methoxy-2-phenylpyrimido[4,5-*b*]quinoline (IV).

A mixture of III (8.3 g.) and phosphorus oxychloride (100 ml.) was heated under reflux for 4 hours, then allowed to set overnight at room temperature. The red crystals thus deposited were collected on a filter under a nitrogen atmosphere, then dried *in vacuo* over potassium hydroxide at 100°. The product weighed 5.0 g. and melted at 206-209° dec. Since this compound was sensitive to moisture and unstable in the atmosphere it was used directly in the subsequent reactions.

Trituration of the red crystalline product with saturated aqueous solution of sodium bicarbonate at room temperature gave 5-hydroxy-7-methoxy-2-phenylpyrimido[4,5-*b*]quinoline (V). The product was recrystallized from DMF. The compound did not melt below 360°; ir: 3.35 (broad, OH); uv λ max (95% ethanol): 297 mμ (2.35×10^4).

Anal. Calcd. for $C_{18}H_{13}N_3O_2$: C, 71.27; H, 4.32; N, 13.86. Found: C, 71.11; H, 4.36; N, 13.91.

When a mixture of V (0.2 g.) and phosphorus oxychloride (5 ml.) was refluxed for 4 hours, then allowed to set overnight at room temperature, there was deposited a red crystalline product (m.p. 208-210° dec.) which is identical with IV prepared from III.

7-Methoxy-5-(2-morpholinoethylamino)-2-phenylpyrimido[4,5-*b*]quinoline (VIIb).

To a solution containing 20 ml. of *N*-(2-aminoethyl)morpholine in 15 ml. of absolute ethanol was added in small portions 4.5 g. of IV. An exothermic reaction took place during the addition. When the reaction temperature began to subside, the mixture was warmed on a steam bath for 1 hour, then poured into 150 ml. of cold water. The precipitate thus formed was collected on a filter, and washed with water several times giving 2.4 g. of product, m.p. 245° dec. Recrystallization from DMF improved the m.p. to 246-248° dec.; ir 3.15 μ (NH); uv λ max (95% ethanol): 298 (3.88×10^4) and 310 (shoulder) mμ (3.62×10^4).

Anal. Calcd. for $C_{24}H_{25}N_5O_2$: C, 69.38; H, 6.07; N, 16.86. Found: C, 69.35; H, 6.16; N, 16.64.

7-Methoxy-5-(2-methoxyethylamino)-2-phenylpyrimido[4,5-*b*]quinoline (VIIa).

This compound was prepared in a similar fashion from IV and methoxyethylamine with 40% yield. The sample melted at 195-197° dec.

Anal. Calcd. for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55. Found: C, 69.73; H, 5.60; N, 15.55.

5-[(2-Dimethylaminoethyl)amino]-7-methoxy-2-phenylpyrimido-[4,5-*b*]quinoline (VIIc).

One and one half g. of IV was added to 10 ml. of 2-dimethylaminoethylamine in small portions, and the resulting mixture was stirred for 0.5 hour, then poured into a large amount of ice water. The precipitate thus formed was collected on a filter, washed with water, and recrystallized from absolute ethanol giving 0.7 g. of product, m.p. 203-205°.

Anal. Calcd. for $C_{22}H_{23}N_5O$: C, 70.75; H, 6.21; N, 18.76. Found: C, 70.69; H, 6.06; N, 18.64.

4-(*p*-Anisidino)-*N*-(2-methoxyethyl)-2-phenyl-5-pyrimidinecarboxamide (VI).

Eight and three-tenths grams of III was added to 100 ml. of phosphorus oxychloride and the resulting mixture was refluxed for 4 hours, then allowed to set overnight at room temperature. The red crystals (IV) thus deposited were removed by filtration, and the filtrate was concentrated *in vacuo*. 2-Methoxyethylamine (50 ml.) was added dropwise with care to the residue under chilling. The resulting mixture was stirred at room temperature for 0.5 hour, then poured into a large amount of ice water, whereby a resinous material was deposited. The supernatant layer wad decanted. Addition of 25 ml. of ethanol to the residue caused crystallization of the resinous material. Recrystallization from absolute ethanol afforded 1.5 g. of product, m.p. 160-162°; ir 3.15 (NH) and 6.10 μ (C=O).

Anal. Calcd. for $C_{21}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.81. Found: C, 66.63; H, 5.70; N, 14.91.

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