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Synthesis of 6-Substituted Pyrimidines by the Wittig Reaction. I (1,2). Via 2-Amino-4-hydroxy-5-phenylbutylpyrimidine-6-carboxaldehyde

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Condensation of isopropyl 6-phenylhexanoate with ethyl diethoxyacetate followed by guanidine afforded 2-amino-6-diethoxymethyl-5-phenylbutyl-4-pyrimidinol (VII). Acid hydrolysis of VII gave an excellent yield of 2-amino-4-hydroxy-5-phenylbutylpyrimidine-6-carboxaldehyde (IV); the latter could be condensed with stabilized Wittig reagents such as carbethoxymethylene triphenyl phosphorane and cinnamylidene triphenyl phosphorane, but not unstabilized Wittig reagents such as carbethoxypropylene or cyanopropylene triphenyl phosphorane. Reduction of the Wittig products afforded pyrimidines with functionalized side-chains in the 6-position such as the 6-phenylbutyl (XVIII) and 6-carboxyethyl (XV) derivatives of 2-amino-5-phenylbutyl-4-pyrimidinol.

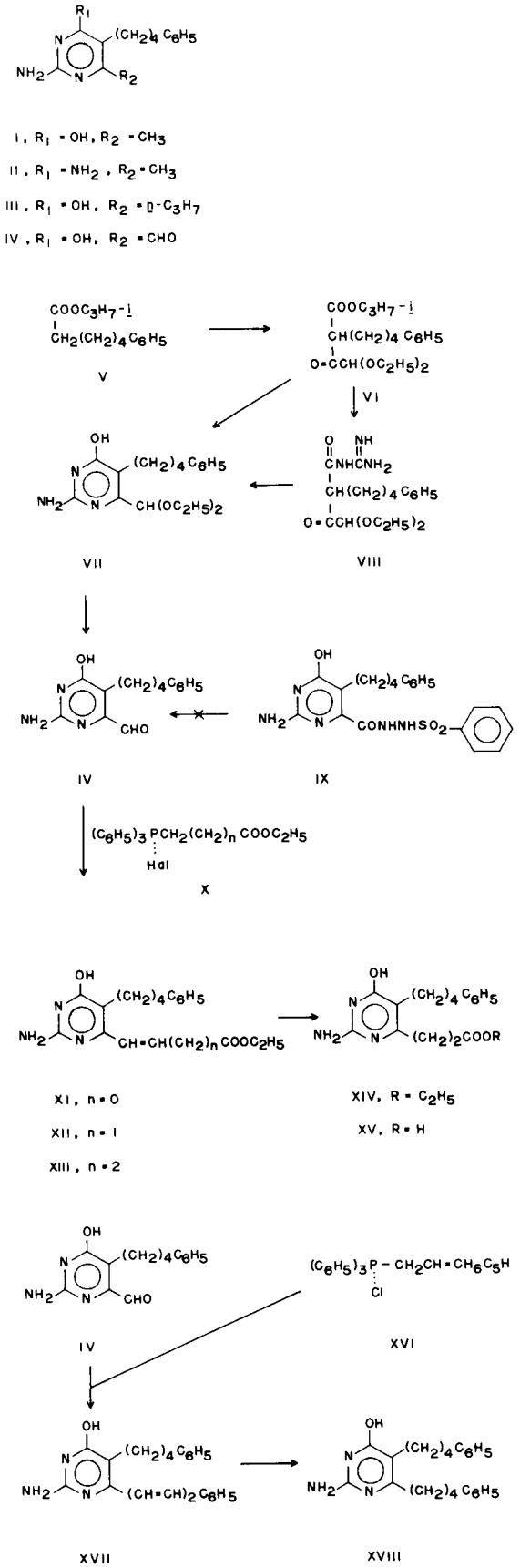
2-Amino-6-methyl-5-phenylbutylpyrimidine bearing a 4-hydroxy group (I) is a reasonably good inhibitor (3) of the enzyme, dihydrofolic reductase, and the corresponding 4-aminopyrimidine (II) is an excellent inhibitor (4). Irreversible inhibitors of this enzyme might be obtained if the R_2 group could be functionalized with an active halogen such as a bromoacetamido or chloromethyl ketone group (5, 6).

2-Amino-4-pyrimidinols substituted with alkyl groups or aralkyl groups at the 5- and 6-positions, such as III (7), can be synthesized by condensation of the appropriate α,γ-disubstituted acetoacetic ester with guanidine (8). Such a synthetic approach has several limitations for synthesis of pyrimidines of type I bearing a functionalized R_2 group; (a) the requisite β-keto ester may be difficult to synthesize due to incompatibility with a functional group on the γ-position, and (b) the functional group on R_2 may not be compatible with pyrimidine formation from the requisite β-keto ester by reaction with the strongly basic guanidine. Furthermore, the possible need for a variety of different functional groups and chain lengths on the R_2 group for enzyme studies would require that the variants would be introduced at an early stage of the synthesis; all of the steps would then have to be repeated each time the R_2 group was changed. Therefore, for the type R_2 variants needed for biological studies it would be convenient if the R_2 variant were introduced near the end of the sequence.

The synthesis of pyrimidine-6-carboxaldehydes are rare (8) and no examples of a Wittig reaction with a pyrimidine-6-aldehyde could be found (9), although other non-functionalized heterocycles have been used (9). If a pyrimidine-6-aldehyde such as IV could be synthesized and if the conditions for the Wittig reaction were compatible with the amphoteric nature and poor solubility properties of IV, an attractive route to the desired R_2 variants of I could emerge. The synthesis of IV and the scope of its utility in transformation by Wittig reagents is the subject of this paper.

In a recent study (6e) on the chemistry of 2-amino-4-hydroxy-5-phenylbutylpyrimidine-6-carboxylic acid, unsuccessful attempts to convert the benzenesulfohydrazide derivative (IX) to the desired pyrimidine-6-carboxaldehyde (IV) by a McFadyen-Stevens reaction (10) were described. A successful route to IV was the following:

Claisen condensation of isopropyl 6-phenylhexanoate (V) (6e) with ethyl diethoxyacetate in benzene in the presence of sodium hydride afforded the β-keto ester (VI) in 93% yield which might have been partially trans-esterified to the ethyl ester; the isopropyl ester (V) was employed to reduce the amount of self-condensation of V (6e). Condensation of the keto ester (VI) with guanidine carbonate in t-butyl alcohol gave two products; the intermediate guanide (VIII) separated from the reaction mixture in 22% yield, and from the filtrate could be isolated the expected pyrimidine acetal (VII) in 20% yield. The guanide could be quantitatively cyclized to the pyrimidine acetal (VII) in hot 0.5 *N* 50% aqueous alcoholic potassium hydroxide. When the guanidine reaction was performed with guanidine hydrochloride and sodium methoxide in boiling ethanol, the intermediate guanide (VIII) gradually redissolved and the pyrimidine acetal could be isolated in 54% yield, a higher overall yield than by the guanidine carbonate two-step method. Hydrolysis of the acetal group of VII with hot 2 *N* hydrochloric acid proceeded smoothly and an 89% yield of analytically pure pyrimidine-6-carboxaldehyde (IV) could be isolated.



Wittig condensation of the pyrimidine-6-carboxaldehyde (IV) hydrochloride with a 2:1 excess of carbethoxymethylene triphenyl phosphorane (11) in refluxing *t*-butyl alcohol proceeded smoothly to give a 58% yield of the analytically pure pyrimidylacrylate (XI); a similar reaction with the free base of IV proceeded in only 38% yield. It is initially surprising that the reaction proceeds better with the hydrochloride of IV than the free base. Apparently the phosphorane is not a stronger base than the aldehyde; if this is the case, then the hydrochloride of IV would be expected to react more efficiently with the phosphorane since the hydrochloride of IV has a more electrophilic aldehyde than does the free base of IV.

Catalytic hydrogenation of the side-chain double bond of XI with a palladium-charcoal catalyst to XIV followed by saponification gave the pyrimidyl-6-propionic acid in 70% overall yield of pure material.

Attempts to condense the higher homologs of X with the pyrimidine-6-aldehyde (IV) under a variety of solvent conditions and base stoichiometry proceeded to a myriad of products, as shown by thin-layer chromatography, none of which was major. Similarly, IV failed to condense with Wittig reagents derived by reaction of triphenylphosphine with several ω-bromonitriles, bromopropylphthalimide, dichloroacetone or phenylpropyl bromide.

The only other type of Wittig reagent that could be successfully condensed with IV was cinnamyl triphenylphosphonium chloride (XVI), a benzylic type; the condensation proceeded in 1:2 *N,N*-dimethylformamide: *t*-butyl alcohol with excess sodium methoxide to give 46% of analytically pure XVII. Catalytic hydrogenation with a platinum oxide catalyst proceeded smoothly to XVIII.

Only those ylides which were stabilized by conjugation (9) with a carbonyl (as in X, n = 0) or a benzene ring (as in XVI) could be successfully condensed with the pyrimidine-6-carboxaldehyde (IV) even though the stabilized ylides are less reactive. An exception was chloroacetonyl triphenylphosphorane (13) which gave a dark mixture that could not be purified, probably due to the sluggishness of the Wittig reaction which gave time for side-reactions to occur involving the active chloroacetyl group. Ylides unstabilized by conjugation (9,10) apparently decomposed much faster than they condensed with IV. Furthermore, non-conjugated ylides are much stronger bases than a conjugated ylide such as carbethoxymethylene triphenylphosphorane; therefore IV hydrochloride in the presence of two mole-equivalents of a non-conjugated ylide would immediately form one mole-equivalent of the phosphonium chloride and the free base of IV with its less electrophilic -- and hence less reactive -- aldehyde.

The more electrophilic is the aldehyde partner in the Wittig reaction, the better the reaction proceeds (9,12). It was reasoned that the N^2-acetyl derivative of IV should give a more electrophilic aldehyde since the electron donor properties of the 2-amino group are neutralized on acetylation (13). Reactions with 2-acetamido-4-hydroxy-5-phenylbutylpyrimidine-6-carboxaldehyde did indeed react

successfully with unstabilized ylides; the results are reported in the accompanying paper (14). Since the 2-acetamidopyrimidine-6-carboxaldehyde was more general in the type of ylides with which it would react, IV was not studied further with other stabilized ylides.

EXPERIMENTAL

Melting points were taken in capillary tubes in a Mel-Temp block; all melting points below 230° are corrected. Infrared spectra were determined in potassium bromide disks, unless otherwise indicated, with a Perkin-Elmer 137 B recording spectrophotometer. Ultraviolet spectra were determined in 10% ethanol, unless otherwise indicated, with a Perkin-Elmer 202 spectrophotometer. Thin layer chromatograms (TLC) were run on Brinkmann silica gel GF and spots were detected by visual examination under ultraviolet light.

Isopropyl α-(4-phenylbutyl)-γ,γ-diethoxyacetoacetate (VI).

To a stirred mixture of 35.1 g. (0.150 mole) of V (6e) and 26.4 g. (0.150 mole) of ethyl diethoxyacetate in 150 ml. of benzene, protected from moisture and cooled to 5-10°, was added 6.64 g. (0.150 mole) of a 55.6% dispersion of sodium hydride in mineral oil over a period of 30 minutes. The mixture was stirred at ambient temperature for 1 hour, then slowly brought to reflux over a period of 30 minutes. A total of 100 ml. was gradually distilled over a period of 1 hour to remove ethanol. The cooled mixture was shaken with 200 ml. of 5% aqueous acetic acid. The layers were separated and the aqueous phase was extracted with two 25-ml. portions of benzene. The combined organic extracts, washed with water and dried with magnesium sulfate, were spin-evaporated *in vacuo*; yield, 51.6 g. (93%) of crude product which contained about 3 g. of the original mineral oil and was likely contaminated with some of the corresponding ethyl ester. The oil gave a purple (λ max 550 mμ) ferric chloride test and had λ max (*p*H 7): 261 mμ; (*p*H 13): 295 mμ (enolic keto ester anion); λ max (film): 5.72 (ester C = O); 5.79, 6.23 (enolic keto ester); 6.70 (phenyl C = C); 8.00, 8.50 (ester C-O-C) 9.12, 9.43, (ether C-O-C); 13.37, 14.30 μ (C_6H_5).

2-Diethoxyacetyl-6-phenylhexanoguanide (VIII).

A mixture of 16.6 g. of crude VI (about 45 mmoles), 4.0 g. (22.5 mmoles) of guanidine carbonate and 50 ml. of *t*-butyl alcohol was refluxed gently with magnetic stirring for 12 hours during which time the product separated. The product was collected on a filter, washed with water, then recrystallized from aqueous 2-methoxyethanol; yield, 3.7 g. (22%), of white crystals, m.p. 194-195°, λ max (EtOH): 237 mμ; λ max 2.96, 3.18 (NH); 5.99 (amide C=O); 6.13, 6.20 (C=N, NH); 9.00, 9.37 (ether C-O-C); 13.31, 14.32 μ (C_6H_5).

Anal. Calcd. for $C_{19}H_{29}N_3O_4$: C, 62.8; H, 8.04; N, 11.6. Found: C, 62.3; H, 8.26; N, 11.8.

The pyrimidine (VII) was isolated from the filtrate as described below.

2-Amino-6-(diethoxymethyl)-5-phenylbutyl-4-pyrimidinol (VII).

(A) To 51.6 g. (about 0.14 mole) of crude VI was added a filtered solution of 13.3 g. (0.14 mole) of guanidine hydrochloride and 7.6 g. (0.14 mole) of sodium methoxide in 50 ml. of ethanol. The mixture was refluxed with stirring for 6 hours; the precipitate (presumably VIII) which separated during the first hour, gradually dissolved to a reddish solution. The cooled solution was poured into 500 ml. of ice water and the mixture was acidified with 10 ml. of glacial acetic acid. The gummy precipitate partially solidified on being rubbed.

The mixture was filtered through a Celite pad and the precipitate was washed with water. The product was extracted from the Celite with hot alcohol; the hot solution was treated with decolorizing carbon, then diluted with hot water to turbidity. After being cooled at 3° for several hours, the mixture was filtered and the product was recrystallized once more from aqueous ethanol; yield, 26.3 g. (54%, 50% overall from V) of white crystals, m.p. 173-174°; λ max (*p*H 1): 269 mμ (ε, 7,800); (*p*H 7): 299 mμ (ε, 5,400); (*p*H 13): 288 mμ (ε, 7,100); λ max 2.93, 2.98, 3.17 (NH, OH); 6.00, 6.07, 6.22, 6.39, 6.71 (NH, C=O, C=C, C=N); 9.00, 9.44 (ether C-O-C); 13.54, 14.35 μ (C_6H_5).

Anal. Calcd. for $C_{19}H_{27}N_3O_3$: C, 66.1; H, 7.88; N, 12.2. Found: C, 66.3; H, 7.85; N, 12.3.

(B) The *t*-butyl alcohol filtered from the preparation of VIII was diluted with 20 ml. of 5% aqueous acetic acid and 50 ml. of water. The product was recrystallized from aqueous ethanol; yield, 3.0 g. (20%) of white crystals, m.p. 173-174°, that were identical with those from preparation A.

(C) A mixture of 1.00 g. (2.86 mmoles) of VIII, 25 ml. of ethanol and 25 ml. of 1 *N* aqueous potassium hydroxide was refluxed for 1 hour; the cooled solution was acidified with 3 ml. of glacial acetic acid, then diluted with 25 ml. of water and chilled; yield, 0.86 g. (97%) of white crystals, m.p. 173-174°, that were identical with those from preparation A.

2-Amino-4-hydroxy-5-phenylbutylpyrimidine-6-carboxaldehyde (IV).

A mixture of 6.0 g. (17 mmoles) of VII and 50 ml. of 2 *N* aqueous hydrochloric acid was refluxed for 4 hours. The solution was spin-evaporated *in vacuo* leaving the hydrochloride of IV. The residue was triturated with 25 ml. of cold water, then dissolved in warm 2-methoxyethanol. The solution was clarified with decolorizing carbon, then poured into 100 ml. of saturated aqueous sodium bicarbonate. The yellow powder was collected on a filter and washed with water. Recrystallization from aqueous ethanol gave 4.2 g. (89%) yellow crystals which had no definite m.p.; λ max (*p*H 1): 269 mμ (ε, 5,700); (*p*H 7): 299 mμ (ε, 4,600); (*p*H 13): 288 (ε, 2,900), 354 mμ (ε, 2,300).

Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.4; H, 6.32; N, 15.5. Found: C, 66.2; H, 6.31; N, 15.3.

Ethyl 3-(2-Amino-4-hydroxy-5-phenylbutyl-6-pyrimidyl)acrylate (XI).

A mixture of 308 mg. (1.00 mmole) of IV hydrochloride, 700 mg. (2 mmoles) of carbethoxymethylene triphenyl phosphorane (11) and 10 ml. of *t*-butyl alcohol was gently refluxed for 3 hours, then cooled and diluted with 25 ml. of water and 10 ml. of 1 *N* aqueous hydrochloric acid. The product was collected on a filter, then washed with water. Three recrystallizations from aqueous 2-methoxyethanol, with use of decolorizing carbon the first time, gave 200 mg. (58%) of nearly colorless crystals that turned bright yellow after being dried. The compound had m.p. 179-180°; λ max (*p*H 1): 233 (ε, 17,700), 315 mμ (ε, 10,000); (*p*H 7): 243 (ε, 19,900), 345 mμ (ε, 7,000); (*p*H 13): 239 (ε, 29,000), 345 mμ (ε, 6,100); λ max 2.89, 3.01 (OH, NH); 5.82 (ester C=O); 5.98, 6.10, 6.25, 6.37, 6.70 (NH, C=O, C=N, C=C); 7.82, 8.50 (ester C-O-C); 13.46, 14.40 μ (C_6H_5).

Anal. Calcd. for $C_{19}H_{23}N_3O_3$: C, 66.9; H, 6.79; N, 12.3. Found: C, 66.8; H, 6.71; N, 12.3.

A similar condensation with 542 mg. (2 mmoles) of the free base of IV and 1.40 g. (4 mmoles) of the phosphorane gave 258 mg. (38%) of product, m.p. 175-177°; with a 1:1 ratio the yield was 214 mg. (31%), m.p. 176-177°.

3-(2-Amino-4-hydroxy-5-phenylbutyl-6-pyrimidyl)propionic Acid (XV).

A solution of 1.00 g. (2.93 mmoles) of XI in 200 ml. of 2-methoxyethanol was shaken with hydrogen at 2-3 atmospheres in the presence of 250 mg. of 5% palladium-charcoal until 1 mole-equivalent was absorbed. The filtered solution was spin-evaporated *in vacuo* and the residual ester (XIV) was recrystallized from aqueous ethanol; yield, 850 mg. (85%) of white crystals, m.p. 97-98°.

A solution of 845 mg. of the ester (XIV) in 30 ml. of 1 *N* aqueous sodium hydroxide was refluxed for 30 minutes, clarified with decolorizing carbon, then acidified with 3 ml. of glacial acetic acid. The product was collected on a filter and washed with water. Two recrystallizations from aqueous 2-methoxyethanol gave 640 mg. (82%) of white crystals, m.p. 183-184°; λ max (*p*H 1): 267 mμ (ε, 8,300); (*p*H 13): 282 mμ (ε, 7,400); λ max 3.0-3.1 (broad OH, NH), 3.0-4.0 (broad acidic OH); 5.85-6.0 (broad), 6.05, 6.50, 6.63, 6.70 (C=O, NH, C=C, C=N); 13.45, 14.33 μ (C_6H_5).

Anal. Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.7; H, 6.71; N, 13.3. Found: C, 64.5; H, 6.53; N, 13.2.

2-Amino-5-phenylbutyl-6-(4-phenyl-1,3-butadien-1-yl)-4-pyrimidinol (XVII).

To a magnetically stirred mixture of 850 mg. (2.77 mmoles) of IV hydrochloride and 1.26 g. (3.03 mmoles) of cinnamyl triphenyl phosphonium chloride (15), 5 ml. of *N,N*-dimethylformamide, and 10 ml. of *t*-butyl alcohol cooled in an ice-bath was added 0.50 g. (9.2 mmoles) of sodium methoxide. After being stirred 30 minutes in the ice-bath and 18 hours at ambient temperature, the mixture was acidified with 3 ml. of glacial acetic acid and diluted with 20 ml. of water. The product was collected on a filter and washed with water. Four recrystallizations from aqueous 2-methoxyethanol, the first with the aid of decolorizing carbon, gave 400 mg. (26%) of a yellow powder that was moved as a single spot on TLC in chloroform-ethanol (4:1). The compound gradually decomposes over 200° without melting and had λ max (*p*H 1): 358 mμ (ε, 25,700); (*p*H 7): 362 mμ (ε, 26,800); (*p*H 13): 324 mμ (ε, 39,000); λ max 2.93, 2.99, 3.03, 3.26 (OH, NH); 6.07, 6.16, 6.32, 6.76 (C=O, NH, C=C, C=N); 13.45, 14.48, 14.57 μ (C_6H_5).

Anal. Calcd. for $C_{24}H_{25}N_3O \cdot {}^1/_2H_2O$: C, 75.7; H, 6.89; N, 11.0.

Found: C, 75.8, 75.8; N, 6.80, 6.85; N, 11.4, 11.4.

2-Amino-5,6-bis-(phenylbutyl)-4-pyrimidinol (XVIII).

A solution of 250 mg. (0.66 mole) of XVII in 100 ml. of 2-methoxyethanol was shaken with hydrogen at 2-3 atmospheres in the presence of platinum oxide catalyst for 18 hours when 2 mole-equivalents of hydrogen were absorbed. The mixture was filtered through a Celite pad and the filtrate was spun-evaporated *in vacuo*. The residual oil was dissolved in acetone, clarified with charcoal, then treated with 5 ml. of 1 *N* aqueous hydrochloric acid and diluted with water to turbidity. After being chilled for several hours, the mixture was filtered and the product washed with water. Recrystallization from a mixture of acetone and 0.1 *N* aqueous hydrochloric acid gave 180 mg. (68%) of white crystals, m.p. 112-114°, which showed one spot on TLC in chloroform-ethanol (5:1). The compound had λ max (*p*H 1): 267 mμ (ε, 9,100); (*p*H 13): 281 mμ (ε, 8,600); λ max 3.03, 3.13 (NH, OH), 3.6-3.9 (broad), 5.36, 5.72 (NH^+); 5.80 ($C{=}NH^+$), 6.10, 6.28, 6.50, 6.63, 6.70 (NH, C=C, C=N, C=O); 13.46, 14.37 μ (C_6H_5). Typical of hydrochlorides of 2-amino-4-pyrimidinols, the compound tends to lose hydrogen chloride on long drying.

Anal. Calcd. for $C_{24}H_{29}N_3O \cdot {}^3/_4HCl$: C, 71.5; H, 7.45; N, 10.4. Found: C, 71.4; H, 7.67; N, 10.1, 10.4.

A solution of 100 mg. of XVIII hydrochloride in ethanol was treated with 1 ml. of 2 *N* sodium hydroxide and diluted with water. The precipitated XVIII was collected and recrystallized from ethanol-water; yield 84 mg., m.p. 129-131°. The compound showed a single spot on TLC in 5:1 chloroform-ethanol.

Anal. Calcd. for $C_{24}H_{29}N_3O \cdot {}^1/_2H_2O$: C, 75.0; H, 7.87; N, 10.9. Found: C, 74.9; H, 8.41; N, 10.6.

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