Department of Chemistry, University of California, Santa Barbara
and
Department of Medicinal Chemistry, State University of New York at Buffalo

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

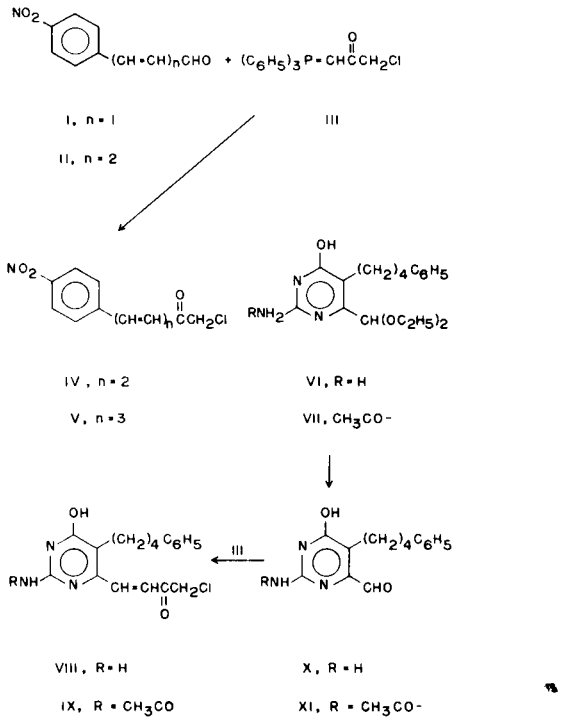
B. R. Baker and Johannes H. Jordaan

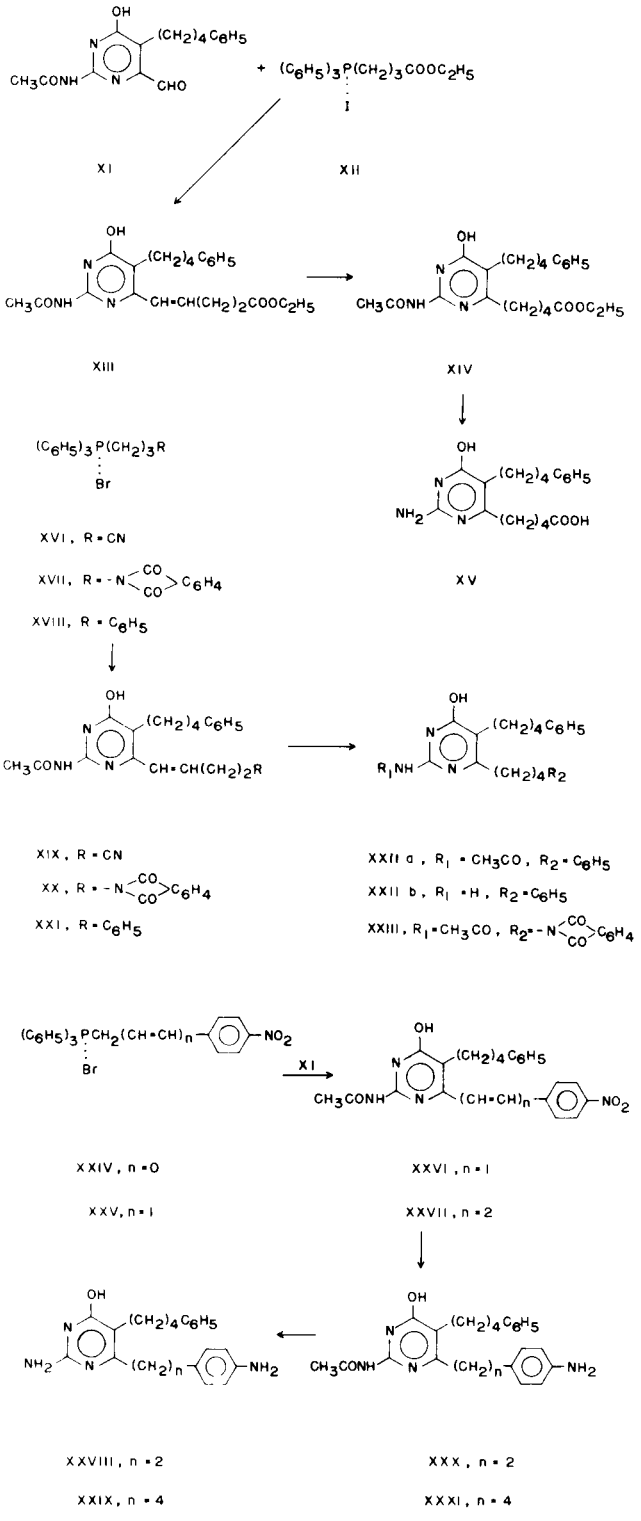
Wittig condensations of both stabilized and unstabilized ylides were successfully achieved with 2-acetamido-4-hydroxy-5-phenylbutylpyrimidine-6-carboxaldehyde (XI); functionalized Wittig reagents derived from dichloroacetone, ethyl 4-iodobutyrate, 4-bromobutyronitrile, phenylpropyl bromide, 3-bromopropylphthalimide, *p*-nitrobenzyl bromide, and *p*-nitrocinnamyl bromide were used. The resultant 6-substituted pyrimidines could be further transformed by reduction of the 6-side-chain double bond. Successful Wittig reactions were achieved with XI where the corresponding 2-amino-4-hydroxy-5-phenylbutylpyrimidine-6-carboxaldehyde (X) with its less electrophilic aldehyde group failed to give isolable yields of condensation products.

In the previous paper of this series (1b), the Wittig reaction with 2-amino-4-hydroxy-5-phenylbutylpyrimidine-6-carboxaldehyde (X) as the aldehyde partner was described. The reaction was successful only with ylides that were stabilized by conjugation (3); unstabilized ylides (3) gave a myriad of products, none of which were major.

The Wittig reaction proceeds best with strongly electrophilic aldehydes (3). For example, Hudson and Chopard (4) studied the condensation of a variety of aldehydes with chloroacetonyl triphenyl phosphorane (III); the yields varied from about 30-48% with high ratios of weakly electrophilic aldehydes such as benzaldehyde, butyraldehyde and furfuraldehyde. In contrast, the strongly electrophilic *p*-nitrobenzaldehyde in only 25% excess gave a 79% yield of Wittig product (4, 5). They rationalized (4) that the poor yields were due to instability; although it is true that these compounds are sensitive, the highly unsaturated chloromethyl ketones, IV and V which could be expected to be even more sensitive were obtained in 64 and 62% yields, respectively by condensation of *p*-nitrocinnamaldehyde (I) or 5-(*p*-nitrophenyl)-2,4-pentadiene-1-al (II) with the chloracetonyl phosphorane (III) (5). Thus, it was noted that *p*-nitrobenzaldehyde in slight excess (4, 5) and the nitroaldehydes, I and II (5) in equivalent amounts to III could be condensed in good yield, but that less electrophilic aldehydes required a 5-10 fold excess to proceed in even poor yield (4).

Since the electron-donating 2-amino and 4-hydroxyl groups of X reduce both the electronegativity of the pyrimidine ring and the electronegativity of the 6-aldehyde, it was reasoned that a more electronegative pyrimidine-6-aldehyde derivative might condense with III more rapidly, thus giving increased yields. Such increased electronegativity has been used previously in certain reactions of pyrimidines and pteridines by conversion of the electron-donating 2-amino group to the neutral acetamido group. For example, Sletzinger, *et al.* (6), noted that 2-acetamino-4-hydroxypteridine-6-carboxaldehyde could be reductively condensed with aromatic amines in the





presence of thiophenol, but the corresponding 2-amino-pteridine failed to reduce. Similarly, it was observed in this laboratory (7) that 2-acetamido-4-pyrimidinols were converted to 2-acetamido-4-chloropyrimidines with phosphorus oxychloride far more rapidly than the corresponding 2-amino-4-pyrimidinols and the resultant 2-acetamido-4-chloropyrimidines were more easily attacked by a nucleophile. The synthesis of 2-acetamido-4-hydroxy-5-phenylbutylpyrimidine-6-carboxaldehyde (XI) and its successful condensation with a variety of stabilized and unstabilized Wittig reagents is the subject of this paper.

Acetylation of VI (1b) with hot acetic anhydride afforded the crystalline 2-acetamidopyrimidine (VII) in 76% yield. The acetal linkage of VII was hydrolyzed selectively without concomitant hydrolysis of the N^2 acetyl group by 97% formic acid at 100° to give a 92% yield of the desired 2-acetamidopyrimidine-6-aldehyde (XI); this reagent has previously been used for such a selective hydrolysis in the pteridine (6) and pyrimidine areas (8).

A Wittig condensation of the 2-acetamidopyrimidine-6-carboxaldehyde (XI) with chloracetonyl triphenylphosphorane (III) in boiling benzene proceeded smoothly to give a 71% yield of pure, colorless chloromethyl ketone, IX; in contrast, a similar reaction with the 2-aminopyrimidine-6-carboxaldehyde (X) gave a brown intractable powder that showed a myriad of spots on thin layer chromatography (1b).

The Wittig reactions between the 2-acetamidopyrimidine-6-carboxaldehyde (XI) and unstabilized ylides (3) were then investigated. Solid potassium *t*-butoxide in reagent tetrahydrofuran was used to prepare the ylide; this base - in contrast to sodium methoxide - will not cleave the N^2-acetyl group of XI. The carbethoxypropyl phosphonium iodide (XII) readily condensed with XI to give a mixture of *cis*- and *trans*-isomers of XIII in 45% yield; one of the isomers was obtained crystalline by preparative thin layer chromatography. When the mixture of *cis-trans* isomers (XIII) was hydrogenated with a platinum oxide catalyst, an 85% yield of one product, namely XIV, was obtained. Simultaneous saponification of both the N^2-acetyl and ester groups of XIV afforded the crystalline pyrimidine-6-valeric acid (XV) in 75% yield.

Three other unstabilized ylides (XVI-XVIII), which failed to give isolable products when condensed with the 2-aminopyrimidine-6-carboxaldehyde (X) (1b), were successfully reacted with the 2-acetamidopyrimidine-6-carboxaldehyde (XI). In the cases of the phenylpropyl (XVIII) and cyanopropyl (XVI) Wittig reagents, the major isomers of XXI and XIX were formed in 29% and 41% yield, respectively; one other minor spot was present in each case which may have been the other isomer. In the case of the phthalimidopropyl Wittig reagent (XVII), two pure isomers of XX were isolated by preparative thin layer chromatography in 41 and 12% yields; due to the complexity of the infrared and NMR spectra from the multitude of groups, configurational assignments could not be made. Reduction of either isomer of XX or the mixture of isomers gave the same 6-(phthalimidobutyl)pyrimidine (XXIII).

Reduction of the 6-(phenylbutenyl)pyrimidine (XXI) to XXIIa followed by hydrolysis gave the 6-phenylbutylpyrimidine (XXIIb) identical with XXIIb prepared by X and a cinnamyl Wittig reagent followed by reduction (1b).

Stabilized Wittig reagents (3) from *p*-nitrobenzyl

TABLE I

Physical Properties of Wittig Reagents Prepared by

$$R\text{-Hal} + (C_6H_5)_3P \longrightarrow R\text{-}\underset{\underset{Hal}{|}}{P}(C_6H_5)_3$$

Compound No.	R-Hal	M.p. °C	% Yield (a)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XII	$I(CH_2)_3COOC_2H_5$ (b)	194-195	69 (c)	57.2	5.20		56.9	5.05	
XVI	$Br(CH_2)_3CN$	224-225	40	64.4	5.16	3.41	64.2	5.20	3.36
XXXII	$Br(CH_2)_4CN$	229-230	45	65.1	5.46	3.30	65.1	5.41	3.19
XXXIII	$Br(CH_2)_5CN$	149-150	46 (c)	65.8	5.75	3.20	65.6	5.90	3.10
XVII	$Br(CH_2)_3\ N\langle^{CO}_{CO}\rangle C_6H_4$	158-160	63	65.7	4.75	2.64	65.7	4.96	2.67
XVIII	$Br(CH_2)_3C_6H_5$	214-215	76	70.3	5.68		70.1	5.75	
XXIV	$BrCH_2C_6H_4NO_2$-*p* (d)	274-275	89						
XXV	$BrCH_2CH{=}CHC_6H_4NO_2$-*p* (e)	170-171	75 (f)	64.3	4.60	2.78	64.1	4.80	2.50

(a) All compounds had infrared spectra in agreement with their assigned structures; no attempt was made to obtain optimum yields. (b) Ethyl 4-chlorobutyrate was converted to the iodo derivative with a two-fold excess of sodium iodide in boiling methyl ethyl ketone for 18 hours. The crude, washed ethyl 4-iodobutyrate was condensed with triphenyl phosphine and the yield is overall for the two steps. (c) The product separated as an oil, but crystallized on trituration with ether. (d) R. N. McDonald and T. W. Campbell, *J. Org. Chem.*, 24, 1969 (1959) reported m.p. 275-275.5° and 95% yield. (e) *p*-Nitrocinnamyl bromide was prepared according to B. Elpern, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, 79, 1951 (1957). (f) Reaction run in boiling 1:1 tetrahydrofuran-benzene for 4 hours.

bromide (XXIV) and *p*-nitrocinnamyl bromide (XXV) also condensed with the 2-acetamidopyrimidine-6-carboxaldehyde (XI); single isomers of XXVI and XXVII were readily crystallized in 44 and 36% yields, respectively, but no attempt was made to isolate a second isomer in either case. Catalytic hydrogenation and hydrolysis afforded the 6-(*p*-aminophenylalkyl) pyrimidines, XXVIII and XXIX, that were identical with these compounds prepared via the 2-amino-6-bromomethyl-4-hydroxy-5-phenylbutylpyrimidine Wittig reagent described in the following paper (9).

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 with a Perkin-Elmer 137 B recording spectrophotometer. Ultraviolet spectra were determined in 10% aqueous ethanol, unless otherwise indicated, with a Perkin-Elmer 202 recording spectrophotometer. Thin layer chromatograms (TLC) were run on Brinkmann silica gel GF and spots were detected by visual examination under ultraviolet light; aldehyde XI was also detected by spraying with dianisidine in glacial acetic acid (10) which gave a yellow color.

3-Cyanopropyl Triphenylphosphonium Bromide (XVI).

A solution of 3.7 g. (25 mmoles) of 4-bromobutyronitrile and 5.2 g. (20 mmoles) of triphenylphosphine in 20 ml. of benzene was refluxed with magnetic stirring for about 18 hours during which time the product separated. The product was collected on a filter and washed with 20 ml. of benzene, then 10 ml. of ether; yield, 3.3 g. (40%), m.p. 224-225°, which was analytically pure and had λ max 4.46 (CN); 6.34, 6.78 (C=C), 9.04 (C-P^+); 13.42, 14.52 μ (C_6H_5).

Other compounds prepared by this method and analytical data are listed in Table I; no attempt was made to obtain optimum yields.

2-Acetamido-4-diethoxymethyl-5-phenylbutyl-4-pyrimidinol (VII).

A solution of 13.8 g. (0.04 mole) of VI (1b) in 50 ml. of acetic anhydride was refluxed for 4 hours, then spin-evaporated *in vacuo*. Recrystallization from ethyl acetate gave 11.7 g. (76%) of white crystals, m.p. 146-147°; λ max (*p*H 1,7): 242 mμ (sh); (*p*H 13): 243, 281 mμ; λ max 3.14 (NH); 5.90 (amide C=O); 6.04, 6.30, 6.50 (NH, C=O, C=C, C=N); 9.05, 9.42 (ether C-O-C); 13.45, 14.45 μ (C_6H_5). The compound moved as a single spot on TLC in 4:1 chloroform-ethanol.

Anal. Calcd. for $C_{21}H_{29}N_3O_4$: C, 65.1; H, 7.54; N, 10.8. Found: C, 65.3; H, 7.53; N, 11.0.

2-Acetamido-4-hydroxy-5-phenylbutylpyrimidine-6-carboxaldehyde (XI).

A mixture of 10 g. (0.026 mole) of VII and 50 ml. of 97% formic acid was heated at 100° for 45 minutes, then spin-evaporated *in vacuo*. Recrystallization of the residue from ethyl acetate-petroleum ether (b.p. 30-60°) gave 7.53 g. (92%) of white crystals, m.p. 176-177°; λ max (*p*H 1): 248 mμ; (*p*H 7): 248, 293 mμ; (*p*H 13): 247, 277 mμ; λ max 2.95, 3.20 (NH); 5.86 (C=O); 6.13, 6.25, 6.44, 6.76 (C=O, C=N, C=C, NH); 13.28, 14.23 (C_6H_5); no acetal C-O-C near 9.05 or 9.42 μ. The compound moved as a single spot on TLC in 4:1 chloroform-ethanol that gave a yellow color with the dianisidine spray for aldehydes (10).

Anal. Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.2; H, 6.11; N, 13.4. Found: C, 65.0; H, 5.94; N, 13.4.

2-Acetamido-6-(4-chloro-3-oxo-1-buten-1-yl)-5-phenylbutyl-4-pyrimidinol (IX).

A mixture of 1.56 g. (5 mmoles) of XI and 1.77 g. (5 mmoles) of

III (4) in 15 ml. of benzene was refluxed with magnetic stirring for 16 hours. The mixture was cooled and the supernatent liquid was decanted from the separated oil. A solution of the oil in ethyl acetate was clarified with decolorizing carbon, then petroleum ether (b.p. 30-60°) was added to the warm solution to turbidity. The crystals that deposited from the cooled solution were collected on a filter. Three additional recrystallizations from the same solvent system gave 1.40 g. (71%) of white crystals, m.p. 139-140°; λ max (*p*H 1): 262, 343 mμ; (*p*H 7): 264, 346 mμ; (*p*H 13): 250, 311 mμ (inflection); λ max 2.95, 3.10 (NH); 5.90, 5.93 (C=O); 6.06, 6.15 (broad), 6.50, 6.75 (NH, C=O, C=C, C=N); 13.45, 14.42 μ (C_6H_5). The compound moved as a single spot on TLC in 5:1 chloroform-ethanol.

Anal. Calcd. for $C_{20}H_{22}ClN_3O_3$: C, 61.9; H, 5.72; N, 10.8. Found: C, 61.8; H, 5.52; N, 10.9.

Ethyl 5-(2-acetamido-4-hydroxy-5-phenylbutyl-6-pyrimidyl-Δ^4-valerate (XIII).

To a magnetically stirred mixture of 0.945 g. (3 mmoles) of XI and 1.513 g. (3 mmoles) of XII in 10 ml. of reagent tetrahydrofuran immersed in an ice-bath and protected from moisture was added 0.672 g. (6 mmoles) of potassium *t*-butoxide. After being stirred for 1 hour at 0°, 24 hours at ambient temperature and 6 hours at reflux, the mixture was acidified with 1 ml. of glacial acetic acid, then diluted with 100 ml. of water. After the stiff oil had settled, the water layer containing most of the triphenyl phosphine oxide was decanted and the oil was rinsed with 20 ml. of water. The dried oil on TLC with chloroform-ethanol (92:8) showed two fast-moving major spots and three slower moving minor spots; one of the slow moving spots corresponded to XI and gave a yellow color when sprayed with dianisidine (10).

A methylene chloride solution of the oil was applied to ten 20 x 20 x 0.15 cm. silica gel PF plates and developed with chloroform-ethanol (92:8); the two fast components moved as single zone. The fast zones were combined and extracted with five 25-ml. portions of hot acetone. The combined extracts were clarified with decolorizing carbon, then spin-evaporated *in vacuo*; yield, 0.626 g. (45%) of XIII as an oily mixture of *cis-trans* isomers which was suitable for further transformation.

In order to separate the *cis-trans* isomers, a methylene chloride solution of 100 mg. was applied to two 20 x 20 x 0.15 cm. silica gel PF plates and developed with chloroform-ethanol (92:8). The zones of faster-moving component from the two plates were combined and extracted with acetone. Evaporation of the acetone *in vacuo* gave an oil that soon crystallized. Recrystallization from ethyl acetate-petroleum ether (b.p. 60-110°) gave 40 mg. (18%) of white needles of one pure isomer, m.p. 90-91°; λ max (*p*H 1, 7): 246, 303 mμ; (*p*H 13): 288 mμ (inflection); λ max 2.94 (NH); 5.82 (ester C=O); 5.95 (amide C=O); 6.05, 6.14, 6.35, 6.45 (NH, C=O, C=C, C=N); 13.33, 14.29 μ (C_6H_5).

Anal. Calcd. for $C_{23}H_{29}N_3O_4$: C, 67.1; H, 7.10; N, 10.2. Found: C, 66.9; H, 7.05; N, 10.0.

Ethyl 5-(2-acetamido-4-hydroxy-5-phenylbutyl-6-pyrimidylvalerate (XIV).

A solution of 500 mg. (1.22 mmoles) of a *cis-trans* mixture of XIII in 50 ml. of ethanol was shaken with hydrogen in the presence of 100 mg. of platinum oxide catalyst until 1 mole-equivalent of hydrogen was absorbed. The mixture was filtered through a Celite pad; the filtrate was spin-evaporated *in vacuo* to an oil which soon crystallized. Recrystallization from chloroform-petroleum ether (b.p. 30-60°) gave 430 mg. (85%) of white crystals, m.p. 100-101°, that were uniform on TLC with chloroform-ethanol (92:8) and had λ max (*p*H 1): 245, 265 mμ (inflection); (*p*H 7): 247 mμ; (*p*H 13): 246, 274 mμ (inflection); λ max 2.94, 3.14, 3.18 (NH); 5.80 (ester C=O); 5.95 (amide C=O); 6.06, 6.14, 6.29, 6.43, 6.71 (NH, C=O, C=C, C=N); 13.28, 14.29 μ (C_6H_5).

Anal. Calcd. for $C_{23}H_{31}N_3O_4$: C, 66.8; H, 7.56; N, 10.2. Found: C, 66.6; H, 7.73; N, 10.0.

5-(2-Amino-4-hydroxy-5-phenylbutyl)-6-pyrimidylvaleric acid (XV).

A solution of 120 mg. (0.29 mmole) of XIV in 5 ml. of 2 *N* aqueous sodium hydroxide was heated at 100° for 30 minutes, then acidified with 2 ml. of glacial acetic acid. The product was recrystallized from aqueous ethanol to give 75 mg. (75%) of white crystals, m.p. 202-203°; λ max (*p*H 1) 223, 268 mμ; (*p*H 13): 230, 280 mμ; λ max 3.18 (NH, OH); 3.00-4.00 (broad), 5.32 (NH^+); 5.92 ($C{=}NH^+$); 5.97, 6.06, 6.47, 6.90, (NH, C=O, C=C, C=N, COO^-); 7.18 (COO^-); 13.46, 14.29 μ (C_6H_5). The infrared spectrum indicated a zwitterion.

Anal. Calcd. for $C_{19}H_{25}N_3O_3$: C, 66.4; H, 7.34; N, 12.2. Found: C, 66.4; H, 7.73; N, 12.2.

2-Acetamido-6-(4-cyano-1-buten-1-yl)-5-phenylbutyl-4-pyrimidinol (XIX).

A mixture of 0.945 g. (3 mmoles) of XI, 1.231 g. (3 mmoles) of XVI, and 0.672 g. (6 mmoles) of potassium *t*-butoxide in 10 ml. of tetrahydrofuran was treated as described for the preparation of XIII. The crude oily product (1.62 g.) on TLC in chloroform-ethanol (92:8) showed one major spot, one minor faster moving spot and two slower moving minor spots; one of the latter was XI (positive dianisidine test (10)). Preparative thin layer chromatography as described for XIII gave 530 mg. (49%) of the major product. Two recrystallizations from ethyl acetate-petroleum ether (b.p. 60-110°) gave 450 mg. (41%) of white crystals, m.p. 109-110°, showing a single spot on TLC; λ max (*p*H 1, 7): 244, 303 mμ; (*p*H 13): 289 mμ; λ max 2.94 (NH); 4.50 (C≡N); 5.81, 5.97, 6.45, (C=O, C=C, C=N, NH); 13.33, 14.29 μ (C_6H_5).

Anal. Calcd. for $C_{21}H_{24}N_4O_2$: C, 69.2; H, 6.64; N, 15.4; O, 9.05. Found: C, 68.1, 68.2; H, 6.25, 6.77; N, 15.7, 15.4; O, 8.78.

The compound is pure by TLC and m.p. criteria and H, N, and O agree with theoretical; however, the found carbon was consistently 1% low. Since the total is only 98.9% it would appear that combustion for carbon was incomplete.

No attempt was made to isolate the minor isomer.

2-Acetamido-5-phenylbutyl-6-(4-phenyl-1-buten-1-yl)-4-pyrimidinol (XXI).

From 0.945 g. (3 mmoles) of XI, 1.384 g. (3 mmoles) of XVIII and 0.672 g. of potassium *t*-butoxide, as described for the preparation of XIII, was obtained 560 mg. (45%) of chromatographically pure major product; no attempt was made to isolate the minor isomer. Two recrystallizations from ethyl acetate-petroleum ether (b.p. 60-110°) gave 365 mg. (29%) of white crystals, m.p. 102-103°; λ max (*p*H 1, 7): 248, 305 mμ; λ max 2.94, 3.09, 3.18 (NH); 5.81, 5.95, 6.06, 6.14, 6.25, 6.67, 6.76 (NH, C=O, C=C, C=N); 13.37, 14.29 μ (C_6H_5).

Anal. Calcd. for $C_{26}H_{29}N_3O_2$: C, 75.1; H, 7.03; N, 10.1. Found: C, 75.0; H, 7.14; N, 10.2.

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

A solution of 470 mg. (1.13 mmoles) of XXI in 50 ml. of ethanol was treated with decolorizing carbon, then shaken with hydrogen in the presence of 100 mg. of platinum oxide catalyst until 1 mole-equivalent of hydrogen was absorbed. The mixture was filtered through a Celite pad, then the filtrate was spin-evaporated *in vacuo*. The residual XXIIa was refluxed in a solution of 10 ml. of ethanol and 10 ml. of 2 *N* aqueous sodium hydroxide for 2 hours, then adjusted to *p*H 4-5 with acetic acid and diluted with 100 ml. of water. The separated product was recrystallized from aqueous ethanol to give 344 mg. (81%) of white crystals, m.p. 144-146°; λ max (*p*H 1): 226 (inflection), 268 mμ; (*p*H 7): 226 (inflection), 293 mμ; (*p*H 13): 230 (inflection), 280 mμ; λ max 3.01, 3.25, 3.28 (NH); 6.12, 6.50, 6.56, 6.76 (NH, C=C, C=N, C=O); 13.33, 13.66, 14.01, 14.35 μ (C_6H_5).

Anal. Calcd. for $C_{24}H_{23}N_3O$: C, 76.8; H, 7.78; N, 11.2. Found: C, 76.5; H, 7.81; N, 11.0.

The product was identical with XXIIb prepared from X and a cinnamyl chloride Wittig reagent, followed by reduction (1b).

2-Acetamido-5-phenylbutyl-6-(4-phthalimido-1-buten-1-yl)-4-pyrimidinol (XX).

To a magnetically stirred mixture of 313 mg. (1 mmole) of XI, 530 mg. (1 mole) of XX in 2 ml. of reagent tetrahydrofuran cooled in an ice-bath and protected from moisture was added 280 mg. (2.5 mmoles) potassium *t*-butoxide. After being stirred for 1 hour at 0°, 1 hour at ambient temperature and 12 hours at reflux, the mixture was spin-evaporated *in vacuo*. The residual oil was dissolved in hot acetone and water was added to turbidity. On being cooled, the solution deposited 400 mg. (82%) of white crystals, m.p. 138-141°, that was a mixture of *cis-* and *trans*-isomers, as shown by TLC with chloroform-ethanol (92:8); this material was suitable for further transformation.

To separate the two isomers, they were applied in acetone solution to six 20 x 20 x 0.125 cm. silica gel plates and developed with chloroform-ethanol (92:8). The zones of faster moving component were combined and extracted with three 25-ml. portions of ethyl acetate. The extracts on evaporation *in vacuo* gave an oil that soon crystallized. Recrystallization from ethyl acetate-petroleum ether (b.p. 30-60°) gave 200 mg. (41%) of one isomer as white needles, m.p. 122-124°; λ max (*p*H 1, 7): 304 mμ; (*p*H 13): 285 mμ (inflection); λ max 2.87, 2.99, 3.10 (NH); 5.64, 5.84 (phthalyl C=O); 6.01, 6.20, 6.46, 6.71, 6.82 (NH, C=O, C=C, C=N); 13.89 (phthalyl CH); 13.38, 14.33 μ (C_6H_5).

Anal. Calcd. for $C_{28}H_{28}N_4O_4$: C, 69.4; H, 5.82; N, 11.6. Found: C, 69.2; H, 5.60; N, 11.7.

The combined zones of slower moving component were extracted with three 25-ml. portions of hot methanol; the combined extracts were evaporated *in vacuo*. Recrystallization from aqueous acetone afforded 60 mg. (12%) of white crystals, m.p. 222-224°, which had an ultraviolet spectrum identical to the faster moving component and had λ max 2.86, 3.10, 3.15 (NH); 5.63, 5.84 (phthalyl C=O, C=C, C=N); 13.87 (phthalyl CH); 13.40, 14.36 μ (C_6H_5).

Anal. Calcd. for $C_{28}H_{28}N_4O_4$: C, 69.4; H, 5.82; N, 11.6. Found: C, 69.2; H, 5.79; N, 11.6.

2-Acetamido-5-phenylbutyl-6-(phthalimidobutyl)-4-pyrimidinol (XXIII).

(A) A solution of 100 mg. of (0.23 mmole) of the *cis-trans* mixture of XX in 50 ml. of ethanol was shaken with hydrogen at 2-3 atmospheres in the presence of 25 mg. of platinum oxide until 1 mole-equivalent of hydrogen was absorbed. The filtered solution was spin-evaporated to dryness *in vacuo* leaving an oil that was crystallized from ethyl acetate-petroleum ether (b.p. 30-60°); yield, 70 mg. (70%) of a low melting dimorph, m.p. 133-135°, that moved as a single spot on TLC in chloroform-ethanol (92:8) with identical mobility to preparation C. Recrystallization from ethyl acetate-petroleum ether (60-110°) by seeding with preparation C gave the high melting dimorph, m.p. 155-158° with softening at 144°, which still had the same mobility on TLC.

(B) A similar hydrogenation of the lower melting isomer of XX gave 75 mg. (75%) of XXIII as the lower melting dimorph, m.p. 138-140°, which moved as a single spot on TLC identical to preparation C.

(C) Hydrogenation of the high melting isomer of XX in the same manner gave 71 mg. (71%) of the higher melting dimorph, m.p. 158-160° with softening at 146°; this compound moved as a single spot on TLC in chloroform-ethanol (92:8). B and C were combined and recrystallized from ethyl acetate-petroleum ether (b.p. 60-110°) to give 108 mg. (54%) of white crystals, m.p. 161-163°; λ max (*p*H 1): 242, 267 mμ (inflection); (*p*H 7): 243, 290 mμ (inflection); (*p*H 13): 243, 271 mμ (inflection); λ max 2.90, 3.17 (NH); 5.69, 5.87 (phthalyl C=O); 5.90, 5.95, 6.21, 6.76 (NH, C=O, C=N, C=C); 13.33, 14.25 (C_6H_5); 13.85 μ (phthalyl CH).

Anal. Calcd. for $C_{28}H_{30}N_4O_4$: C, 69.1; H, 6.21; N, 11.5. Found: C, 69.1; H, 6.46; N, 11.4.

2-Acetamido-6-(*p*-nitrostyryl)-5-phenylbutyl-4-pyrimidinol (XXVI).

Condensation of 0.945 g. (3 mmoles) of XI with 1.435 g. (3 mmoles) of XXIV, and described for the preparation of XIII, gave a yellow oil that was crystallized directly. Three recrystallizations from ethyl acetate-petroleum ether (b.p. 30-60°) afforded 570 mg. (44%) of yellow crystals, m.p. 205-206°; λ max (*p*H 1, 7): 261, 331, 358 mμ; (*p*H 13): 250, 361 mμ; λ max 2.94, 3.17 (NH); 6.06, 6.12, 6.23, 6.33, 6.45, (NH, C=O, C=C, C=N) 6.64, 7.52 (NO_2); 12.05 (*p*-C_6H_4); 13.33, 14.29 μ (C_6H_5). The compound moved as a single spot on TLC in chloroform-ethanol (92:8).

Anal. Calcd. for $C_{24}H_{24}N_4O_4$: C, 66.6; H, 5.59; N, 12.9. Found: C, 66.5; H, 5.72; N, 12.8.

No attempt was made to isolate the other isomer.

2-Acetamido-6-(*p*-aminophenethyl)-5-phenylbutyl-4-pyrimidinol (XXX).

A solution of 300 mg. (0.7 mmole) of XXVI in 50 ml. of ethyl acetate was shaken with hydrogen in the presence of 50 mg. of platinum oxide until 4 mole-equivalents of hydrogen were absorbed. The solution was filtered through a Celite pad, then spin-evaporated *in vacuo*. Recrystallization of the residue from ethyl acetate-petroleum ether (b.p. 60-110°) gave 180 mg. (64%) of colorless crystals, m.p. 172-173°; λ max (*p*H 1): 248, 265 mμ (sh); (*p*H 13): 240, 275 mμ (sh); λ max 2.92, 2.99, 3.15, 3.18, 3.26 (NH); 5.95 (amide C=O); 6.13, 6.19, 6.45, 6.67 (NH, C=O, C=C, C=N); 12.12 (*p*-C_6H_4); 13.26, 14.23 μ (C_6H_5).

Anal. Calcd. for $C_{24}H_{28}N_4O_2$: C, 71.3; H, 6.98; N, 13.9. Found: C, 71.4; H, 7.17; N, 13.9.

Hydrolysis of N^2-acetyl group of XXX as described for XXIIb, gave an 85% yield of XXVIII, m.p. 77-79°, that was identical with this compound prepared by another route (9).

2-Acetamido-6-[4-(*p*-nitrophenyl)-1,3-butadien-1-yl]-5-phenylbutyl-4-pyrimidinol (XXVII).

This compound was prepared as described for XXX. Two recrystallizations from ethyl acetate-petroleum ether (b.p. 60-110°) gave 495 mg. (36%) of orange crystals, m.p. 210-212°; λ max 25% EtOH (*p*H 1): 275, 382 mμ; (*p*H 7): 385 mμ; (*p*H 13): 390 mμ; λ max 3.17 (NH); 6.06, 6.12, 6.23, 6.33, 6.46 (NH, C=O, C=C, C=N); 6.64, 7.52 (NO_2); 12.04 (*p*-C_6H_4); 13.32, 14.28 μ (C_6H_5). The compound moved as a single spot on TLC in chloroform-ethanol (92:8).

Anal. Calcd. for $C_{26}H_{26}N_4O_4$: C, 68.1; H, 5.72; N, 12.2. Found: C, 67.9; H, 5.86; N, 12.1.

No attempt was made to isolate the second isomer.

2-Amino-6-(*p*-aminophenylbutyl)-5-phenylbutyl-4-pyrimidinol (XXIX).

A solution of 250 mg. (0.55 mmole) of XXVII in 100 ml. of ethanol was shaken with decolorizing carbon, then filtered. The solution was shaken with hydrogen for 8 hours at 2-3 atmospheres in the presence of 30 mg. of platinum oxide catalyst; since reduction had ceased before completion, the mixture was filtered, then shaken with hydrogen at 2-3 atmospheres in the presence of 25 mg. of fresh platinum oxide, reduction being complete in 8 hours. The mixture was filtered through a Celite pad and the colorless filtrate was spin-evaporated *in vacuo*.

The residual oily XXXI was refluxed in a solution of 10 ml. of ethanol and 5 ml. of 2 *N* aqueous sodium hydroxide for 90 minutes. The solution was diluted with 25 ml. of water, then adjusted to *p*H 5-6 with 10% acetic acid. The product was collected on a filter and recrystallized three times from aqueous ethanol to give 130 mg. (61%) of slightly pink crystals, m.p. 100-102° with softening at 90°; this compound was identical with XXIX prepared by another route (9).

REFERENCES

(1a) Paper XXXVII of the series on Analogs of Tetrahydrofolic Acid; (b) For the previous paper of this series see B. R. Baker and J. H. Jordaan, *J. Heterocyclic Chem.*, 3, 315 (1966).

(2) This work was supported in part by grant Nos. CA-05867, CA-06624, and CA-08695 from the National Cancer Institute, U. S. Public Health Service. J.H.J. is indebted to the Republic of South Africa Atomic Energy Board for a fellowship.

(3) For recent reviews of the Wittig reaction see A. Maercker in "Organic Reactions," A. C. Cope, Ed., John Wiley and Sons, Inc., New York, N. Y., 1965, Vol. 14, pp. 270-490; (b) H. J. Bestman, *Angew. Chem. Intern. Ed. Engl.*, 4, 583, 646 (1965).

(4) R. F. Hudson and P. A. Chopard, *J. Org. Chem.*, 28, 2446 (1963).

(5) B. R. Baker and J. H. Jordaan, *J. Med. Chem.*, 8, 35 (1965); paper XVII of this series.

(6) M. Sletzinger, D. Rheinhold, J. Grier, M. Beachem, and M. Tishler, *J. Am. Chem. Soc.*, 77, 6365 (1955).

(7a) B. R. Baker, C. E. Morreal, and B.-T. Ho, *J. Med. Chem.*, 6, 658 (1963); paper VIII of this series; (b) B. R. Baker and B.-T. Ho, *J. Pharm. Sci.*, 53, 1457 (1964), paper XV of this series; (c) B. R. Baker and P. I. Almaula, *J. Heterocyclic Chem.*, 1, 263 (1964); paper XIX of this series.

(8) J. I. DeGraw, L. Goodman and B. R. Baker, *J. Org. Chem.*, 26, 1156 (1961); paper III of this series.

(9) B. R. Baker and J. H. Jordaan, *J. Heterocyclic Chem.*, 3, 324 (1966); paper XXXVIII of this series.

(10) F. Feigl, "Spot Tests," Elsevier Publishing Co., New York, N. Y., 1960, 6th edition, p. 225.

Received July 12, 1966 Santa Barbara, California 93106