Novel Amination Reactions of Dihydrofurano[2,3-*d*]pyrimidines (1)

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Although alkoxypyrimidines can be aminated to yield aminopyrimidines, monoamination of 2,4- or 4,6-chloroalkoxypyrimidines results in chlorine displacement. Preferential alkoxy displacement in such systems is unusual. We now have evidence of such a displacement in the dihydrofurano[2,3-*d*]pyrimidines (V). In some cases two types of products, formed by displacement of either the chlorine or alkoxy substituent, were obtained.

Pyrimidines with halogen substituents in the active (2,4 or 6) positions undergo a great variety of nucleophilic reactions (3). It is well known that hydroxy, alkoxy and oxo groups will deactivate halogen substituents in pyrimidines (3); nevertheless, aminations of this type are known when more strenous conditions are utilized (4,5). Alkoxy groups may also be displaced by ammonia or other amines to generate aminopyrimidines but this reaction occurs less readily than displacement of corresponding chlorine atoms (3). Alkylthio derivatives of chloropyrimidines show the same general result -- that the chlorine atoms are more reactive to nucleophilic displacement than the alkylthio groups (6,7).

Fused ring pyrimidine systems may give different results, however. Robins (8) has found that in the case of 4-methoxy or 4-methylmercapto-6-chloropyrazolo[3,4-*d*]-pyrimidines, the alkoxy or alkylmercapto groups were preferentially displaced by aqueous methylamine, alcoholic ammonia, or aqueous hydroxide. Robins attributes this abnormal reactivity to activation of the 4-substituents by the chlorine atom at position "6" (the 2-chlorine of the pyrimidine ring). We have found a similar result in a different fused ring pyrimidine system, offering a chlorine at position-4 and an alkoxy group at position-6 to nucleophilic displacement, but lacking the "activating" 2-chlorine.

The chloropyrimidines were prepared by the sequence outlined in Chart I, starting with the commercially available isobutyrophenone. The lactone I was prepared by a Knoevenagel condensation with malononitrile using the procedures of Mowry (9) and Cope and co-workers (10) followed by cyclization in PPA according to our previously described procedure (11-12) in good yield. The dehydration of I to form II with phosphorus oxychloride has been described (13a). α-Cyano-γ-lactones are susceptible to rearrangements in basic media yielding *o*-aminocarbonyldihydrofurans (14-15), and rearrangement of II in ammonium hydroxide proceeded quite smoothly to produce the corresponding 2-amino-4,5-dihydrofuran-3-carboxamide III in good yield as previously described (13b). Treatment of III with ethyl orthoformate (16) yielded the dihydrofurano[2,3-*d*]pyrimidone, IV. Curiously, some difficulty was encountered in the conversion of IV to the chloro derivative V. Usually, reaction with phosphorus oxychloride is sufficient for chlorination (3) but in this case no desired product was obtained. A mixture of phosphorus oxychloride and either dimethylaniline or diethylaniline (3) was also unproductive. A mixture of phosphorus oxychloride and phosphorus pentachloride, a more powerful chlorinating agent (17), gave a mixture of products, undoubtedly containing some *C*-chlorinated by-products, as is usual for this type of reaction. Chlorination with strong acid catalysts (sulfuric acid and chlorosulfonic acid) has been reported (18,19) and utilization of phosphorus oxychloride in sulfuric acid afforded some of the desired product but decomposition products made isolation tedious, A milder acid was indicated and when acetic acid was employed, the chlorination proceeded quite nicely to the desired chloro derivative.

Nucleophilic displacements by amines were carried out employing the conditions suggested and summarized by Brown (3). When V was refluxed with 40% aqueous methylamine, the expected 4-methylamino derivative VIa was obtained in good yield. Concentrated ammonium hydroxide under the same conditions returned only starting material which is not surprising since ammonia is a weaker base and more volatile at refluxing temperatures. When ammonium hydroxide was utilized at an elevated temperature and pressure (sealed tube reaction) the 4-amino derivative VIb was isolated. In an attempt to improve the yield, a saturated methanolic ammonia solution was employed under the same general reaction conditions. The isolated product VIIa, however, exhibited different characteristics. The product analyzed for $C_{14}H_{14}N_3Cl$ while the infrared spectrum showed no NH_3^+ but did show the presence of a primary amine. The lack of NH_3^+ was verified by the fact that the product was not

TABLE I

Comparative Spectral Properties of V, VIb, and VIIa

Compound	Type of Spectra		
	IR (in μ) (a)	UV (in mμ) (b)	NMR (in ppm) (c)
V	6.28 (py C=N) 9.85 (COC)	225 (sh) ϵ = 7,000 263 ϵ = 6,100	8.51 (1H-S), 7.27 (5H-M), 4.38 (1H-S), 1.65 (3H-S), 1.10 (3H-S)
VIb	2.92 (NH_2), 6.03 (NH_2) 9.83 (COC)	248 ϵ = 4,250	8.21 (1H-S), 7.20 (5H-M), 4.71 (2H-S), 4.23 (1H-S), 1.62 (3H-S), 0.98 (3H-S)
VIIa	2.98 (NH_2), 6.10 (NH_2), 6.24 (C=C)	235 ϵ = 19,800 280(sh) ϵ = 6,250	8.23 (1H-S), 7.24 (5H-S), 5.54 (2H-M), 1.89 (3H-S), 1.71 (3H-S),

(a) Potassium bromide mull. (b) 95% Ethanol solvent. (c) Deuteriochloroform solvent, TMS as an internal reference standard. Spectra recorded on Varian Model A-60.

water soluble. In addition, the ultraviolet spectrum was not similar to either the starting material or VIb, and its NMR spectrum was markedly different. The spectral data are summarized in Table I. Structure VIIa is consistent with the spectral data and the chemical characteristics of this product.

The formation of compounds of structure VII from V represents a displacement of a 6-alkoxy group in preference to displacement of the 4-chlorine atom on a chloropyrimidine. Attempts were, therefore, directed at ascertaining the scope and limitations of this novel reaction.

Treating V with a variety of amines resulted in isolation of products only of the types VI or VII. Amines of type VI were obtained when either: (a) methylamine in water or methanol; (b) dimethylamine in water or methanol; (c) ammonium hydroxide; or (d) γ-diethylaminopropylamine or δ-diethylamino-α-methylbutylamine neat, were employed. Products of type VII were isolated when either: (a) γ-diethylaminopropylamine in (i) no solvent, (ii) dimethylformamide of (iii) 50% aqueous isopropanol solvents; (b) methanolic ammonia, were used. The results of these condensations are summarized in Chart I. The spectral data are summarized in Tables II and III. It should be pointed out that compounds of type VI are almost completely devoid of any ultraviolet absorption at greater than 280 mμ while compounds of type VII show a shoulder at 280-285 mμ with an extinction coefficient of approximately 4,000.

There are a number of possible variables such as basi-

CHART I

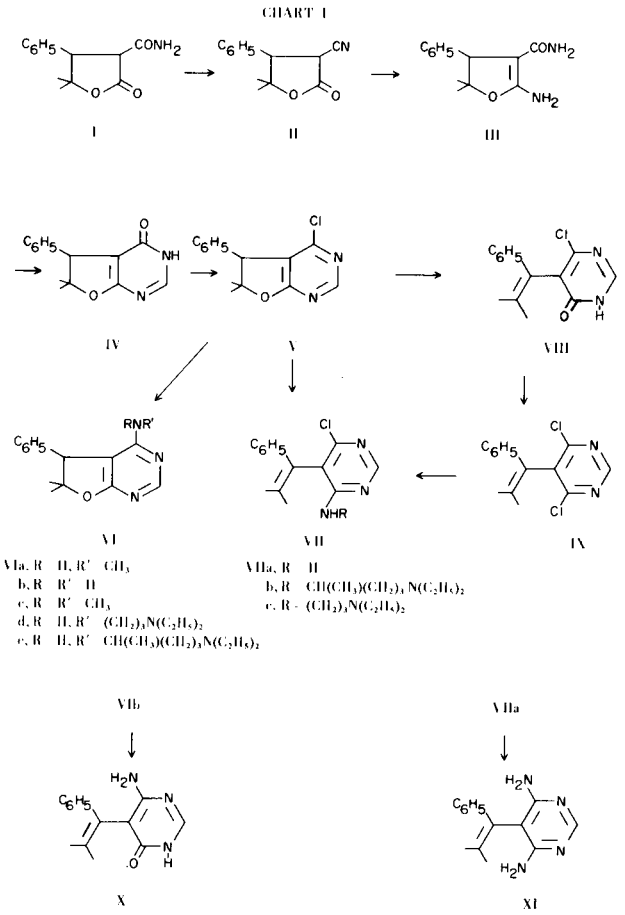
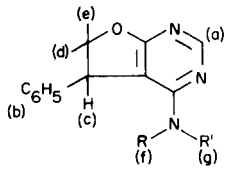
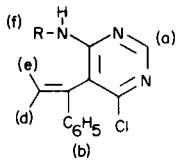


TABLE II

NMR Data of Products VI and VII



VI



VII

Compound	Chemical Shift (a)						
	a	b	c	d	e	f (c)	g
VIa (b)	8.28(S)	7.20(M)	4.21(S)	1.61(S)	0.97(S)	3.88(Q)	2.88(D)
b	8.21(S)	7.21(M)	4.23(S)	1.62(S)	0.98(S)	4.71(M)	4.71(M)
c	8.28(S)	7.11(M)	4.36(S)	1.60(S)	0.98(S)	2.94(S)	2.94(S)
VIIa	8.23(S)	7.24(S)	--	1.89(S)	1.71(S)	5.54(M)	
b	8.26(S)	7.22(S)	--	1.93(S)	1.71(S)	Too complex to resolve	
c	8.25(S)	7.21(S)	--	1.92(S)	1.70(S)	3.50(Q),	2.46(Q) (J=7 cps),
						2.40(M),	1.62(M),
						0.92(T)	(J=7 cps).

(a) NMR spectra recorded at 60 Mc in deuteriochloroform with TMS internal reference standard. (b) Number of protons deleted for clarity but are in agreement. (c) All R protons of VII are listed under f and g for convenience.

city, temperature, solvent, steric size of amines and stereochemistry of the substrate which might explain the unique reactions. However, treatment of V with γ-diethylaminopropylamine under a variety of solvent conditions resulted in nearly identical yields of VIIc in one series of experiments, summarized in Table IV.

In one case, ammonia, a change in solvent gave two different results. Heating V in a sealed glass tube with concentrated aqueous ammonia at 125° for 24 hours produced VIb in 65% yield, while a similar experiment, using saturated methanolic ammonia at 110° for 6 hours gave VIIa in 75% yield. However, a similar solvent change for reactions with methylamine or dimethylamine gave only products of type VI in either solvent.

Some experiments were conducted to explain the anomalous results described above. The possibility that chlorination of IV produced some IX as a possible intermediate of compounds VII was discarded when it was shown that treatment of IV with phosphorus oxychloride and acetic acid for 2½ hours at 140° did not afford any compound IX after chromatography of the crude V. Furthermore the possibility of contamination of V by IX is not likely since a simple melting point depression ought to be observed where the two compounds differ in m.p. by nearly 40° (113-114° vs 72-73°) but such was not the case. The second alternative was the following: If V initially underwent amination at C_4 to give the 4-amino derivative VIb, the by-product ought to be ammonium chloride which conceivably could cause subsequent displacement of the oxygen at C_6 with the overall result appearing to be an abnormal substitution. To test this, V was treated at 100-110° in a bomb with methanolic ammonia containing a mole equivalent of ammonium chloride. The products isolated were V (starting material) and VIb but no desired VIIa. Similarly, VIb, treated in a like manner with methanol and ammonium chloride, only resulted in reisolation of the starting material. Since the p*K* of ammonia is 4.75 and the p*K* of pyridine is 8.77, the corresponding hydrochlorides ought to have about the same relative difference in p*K* (ca. 4 p*K* units). With this in mind, it was decided to employ pyridine hydrochloride in place of ammonium chloride to carry out the conversion of V → IX (the dichloro derivative). Pyridine hydrochloride has been employed to cleave aromatic ethers to phenols (20,21,22). When V was heated as a neat mixture with an equimolar amount of pyridine hydrochloride at 180°, the 4-oxo-6-chloro compound VIII (in 77% yield) was isolated instead of the desired IX. This former compound was characterized by its ir spectrum at 5.93 μ, (C=O sharp) and absence of the furano absorption and elemental analysis. In addition its uv spectrum was similar to the well characterized styryl derivatives VII (see Table

III). Compound VIII, in turn, could be converted to the desired dichloroderivative IX in 64% yield, but under more strenuous conditions than those required for conversion of IV → V. Refluxing phosphorus oxychloride and acetic acid for at least 75 minutes at 110° was required (versus 15-20 minutes at 95-100° for formation of V). The melting point of this dichloro compound is 40° lower than the monochloro derivative, a common phenomena in pyrimidine chemistry. Verification of structure IX was obtained by treatment with methanolic ammonia, which generated the desired chloro-amino derivative VIIa in excellent yield. The melting point and ir spectrum were identical to the previously characterized product.

Attention was then turned to the possibility that VIb would undergo transformation to VIIa employing the previously described techniques with pyridine hydrochloride. The product, obtained in low yield, was an extremely high melting compound, characteristic of oxo-amino pyrimidines, and had the correct analysis and spectral characteristics of X.

These reactions provide a synthetic pathway for the formation of 5-(β,β-dimethyl-α-styryl)-4,6-diaminopyrimidines of possible antimalarial interest. Thus, compound VIIa on treatment with aqueous ammonia gave the 2,6-diamine XI in 80% yield.

TABLE III

UV Spectra of Compounds VI and VII (a)

Compound	λ max (Ethanol) (mμ)	ε
VIa	254	9,950
b	248	4,250
c	263	15,100
VIIa	235	19,800
	280 (sh)	6,250
b	250	16,700
	285 (sh)	4,200
c	248	14,600
	285 (sh)	3,900

(a) Spectral data were recorded on a Cary 14 Spectrophotometer using 95% ethanol as solvent.

TABLE IV

Solvent and Temperature Effects of Aminolysis of V → VIIc

	Solvent	Time (hr.)	Temp. (°C)	% Yield (a)
1.	none	2	165	56
2.	none	12	170	56
3.	$HCON(CH_3)_2$	9	150	48
4.	1:1 H_2O-*i*-C_3H_5OH	20	100	43

(a) The products are very high boiling, viscous liquids which undergo some thermal decomposition on distillation, resulting in low yields.

EXPERIMENTAL

All melting points reported were obtained from a Meltemp capillary melting point apparatus and are corrected. The microanalyses were preformed by Midwest Microlab, Inc., Indianapolis, Indiana. Infrared spectra were recorded with a Perkin-Elmer Model 137 or 137A Infracord. The ultraviolet spectra were recorded using either a Bausch and Lomb Model 505 Spectrophotometer or Cary 14 Spectrophotometer. The NMR spectra were recorded on a Varian Model A-60 spectrometer, employing tetramethylsilane as an internal reference. All NMR spectra were in agreement with the assigned structures.

5-Phenyl-6,6-dimethyl-5,6-dihydro-3*H*-furano[2,3-*d*]pyrimidine-4-one (IV).

A mixture of 30 g. (0.13 mole) of 2-amino-5,5-dimethyl-4-phenyl-4,5-dihydrofuran-3-carboxamide (III) (13b) and 180 ml. of ethyl orthoformate was heated for 3 hours at reflux, the ethanol formed in the reaction being removed continuously by distillation. The reaction mixture was then cooled to 0° overnight during which the product precipitated as a white solid. The product was collected by vacuum filtration, washed with a small amount of ether and dried at reduced pressure, giving 30 g. of product. Recrystallization from 95% ethanol afforded 28.4 g. (90%) of colorless crystals, m.p. 178-179°; λ max (potassium bromide), 5.95 μ (CONH) and 6.22 μ (C=C); λ max (ethanol), 211 mμ (ε = 18,300), 243 mμ (ε = 6,200), 270 mμ (sh) (ε = 5,900) and 275 mμ (ε = 6,000). The NMR spectrum (trifluoroacetic acid), 8.05 δ (1H-S), 7.18 δ (5H-M), 4.28 δ (1H-S), 1.58 δ (3H-S), and 0.95 δ (3H-S).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.57. Found: C, 69.75; H, 6.14; N, 11.37.

5-Phenyl-6,6-dimethyl-5,6-dihydro-4-chlorofurano[2,3-*d*]pyrimidine (V).

To a round bottom flask containing 70 g. (0.29 mole) of IV was carefully added 260 ml. of phosphorus oxychloride followed by 8 ml. of glacial acetic acid. The resulting mixture was refluxed for 1 hour and the excess phosphorus oxychloride removed at reduced pressure. The reaction mixture was cooled to room temperature and poured slowly (in portions) into a 4 l. beaker containing 1 kg. of crushed ice. After stirring for 15 minutes, concentrated ammonium hydroxide was carefully added in portions with continous stirring until the solution was basic to litmus paper. After chilling in the refrigerator overnight, the precipitated solid was collected by filtration, washed with a small amount of water, air dried and recrystallized from 95% ethanol giving 59 g. (78%) of nearly analytically pure crystals bearing a characteristic sweet smell. A second recrystallization from 95% ethanol gave an analytically pure sample of colorless crystals, m.p. 114-116°; λ max (potassium bromide), 6.28 μ (pyrimidine C=N), 9.85 μ (COC); λ max (ethanol), 263 mμ (ε = 6,100) and 225 mμ (sh) (ε = 7,000). The NMR spectrum (deuteriochloroform), 8.54 δ (1H-S), 7.18 δ (5-HM), 4.40 δ (1H-S), 1.65 δ (3H-S) and 1.10 δ (3H-S).

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.50; H, 5.03; N, 10.75. Found: C, 64.45; H, 4.97; N, 10.75.

5-Phenyl-6,6-dimethyl-4-methylamino-5,6-dihydrofurano[2,3-*d*]-pyrimidine (VIa).

A mixture of 6.20 g. (0.0238 mole) of V and 150 ml. of a 40% aqueous methylamine solution was refluxed for 16 hours, after which the reaction mixture was concentrated to one-quarter its initial volume and cooled. The resulting white precipitate obtained was collected by filtration, washed with a small volume of water and dried at reduced pressure over phosphorus pentoxide, giving

5.9 g. of solid. The product was dissolved in hot ethyl acetate, hexane added (3 volumes) and allowed to cool to yield 5.4 g. (89%) of colorless crystals, m.p. 138-140°; λ max (potassium bromide), 3.06 μ (NH), 6.28 μ (pyrimidine C=N) and 9.85 μ (COC); λ max (ethanol), 252 mμ (ε = 9,950). The NMR spectrum (deuteriochloroform), 8.28 δ (1H-S), 7.20 δ (5H-M), 4.21 δ (1H-S), 3.88 δ (1H-M), 2.88 δ (3H-D), 1.61 δ (3H-S), and 0.97 δ (3H-S). A repetition of the above experiment, using methanol saturated with anhydrous methylamine gave the same product in 82% yield.

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.60; H, 6.70; N, 16.45. Found: C, 70.47; H, 6.76; N, 16.45.

4-Amino-6,6-dimethyl-5-phenyl-5,6-dihydrofurano[2,3-*d*]pyrimidine (VIb).

A heterogeneous mixture of V (5.4 g., 0.021 mole) and 80 ml. of concentrated ammonium hydroxide were heated in a sealed bomb at 125° for 24 hours. After cooling, the basic solution was extracted 3 times with chloroform, the combined organic extracts were washed with water and dried (magnesium sulfate). Concentration at reduced pressure afforded about 4 g. of crude product (m.p. 185-187°) which was recrystallized from aqueous methanol to yield 3.2 g. (65%) of white crystals, m.p. 192.5-194°; TLC on silica gel with chloroform gave R_f = 0.05; λ max (potassium bromide), 2.92 μ (NH_2), 6.03 μ (1° NH) and 9.83 μ (COC); λ max (ethanol), 248 mμ (ε = 4,200). The NMR spectrum (deuteriochloroform), 8.21 δ (1H-S), 7.20 δ (5H-M), 4.71 δ (2H-M), 4.23 δ (1H-S), 1.62 δ (3H-S), and 0.98 δ (3H-S).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.70; H, 6.27; N, 17.42. Found: C, 69.73; H, 6.55; N, 17.71.

4-Dimethylamino-5-phenyl-6,6-dimethyl-5,6-dihydrofurano[2,3-*d*]-pyrimidine (VIc).

(a) A homogeneous solution of 5 g. (0.019 mole) of V and 100 ml. of 13% methanolic dimethylamine was heated for 6 hours at 110-120° in a bomb. After cooling, the contents were transferred to a round bottom flask and concentrated at reduced pressure to dryness. The solid residue was triturated with 50 ml. of 5% potassium hydroxide solution and extracted with three small portions of chloroform. The combined extracts were washed with water, dried (magnesium sulfate) and concentrated at reduced pressure affording 4.7 g. of crude product which was recrystallized from ethyl acetate and hexane to yield 4.3 g. (83%) of colorless crystals, m.p. 140.5-142°; λ max (potassium bromide), 6.26 μ (pyrimidine C=N); λ max (ethanol), 262 mμ (ε = 15,100). The NMR spectrum (deuteriochloroform), 8.28 δ (1H-S), 7.11 δ (5H-M), 4.36 δ (1H-S), 2.94 δ (6H-S), 1.60 δ (3H-S), and 0.98 δ (3H-S).

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.36; H, 7.11; N, 15.60. Found: C, 71.43; H, 7.38; N, 15.80.

(b) A heterogeneous mixture of 5 g. (0.019 mole) of V and 100 ml. of 25% aqueous dimethylamine was heated in a bomb at 120-125° for 16 hours. After cooling, the product was extracted with chloroform, the organic solution was washed with water, dried (magnesium sulfate) and concentrated at reduced pressure to yield 4.9 g. of crude solid. The product was recrystallized from ethyl acetate and hexane yielding 4.6 g. (89%) of colorless crystals identical in all respects to that obtained in part (a).

5-Phenyl-6,6-dimethyl-4-(γ-diethylaminopropylamino)-5,6-dihydrofurano[2,3-*d*]pyrimidine (VId).

A mixture of 1.30 g. (0.005 mole) of V and 0.65 g. (0.005 mole) of γ-diethylaminopropylamine in a round bottom flask was heated with stirring in an oil bath at 170° for 12 hours. The reaction mixture was dissolved in 20 ml. of hot 20% acetic acid, cooled, made alkaline by addition of sodium hydroxide pellets and extracted with ether three times. The combined organic layers were washed with a small volume of water, dried (magnesium sulfate) and the filtrate condensed to a yellow oil. Distillation gave 1.0 g. (56%) of product at 285-290°/0.15 mm.; λ max (neat), 3.02 μ (NH) and 6.26 μ (pyrimidine C=N).

Anal. Calcd. for $C_{21}H_{30}N_4O$: C, 71.16; H, 8.52; N, 15.81. Found: C, 71.15; H, 8.62; N, 15.70.

5-Phenyl-6,6-dimethyl-4-(δ-diethylamino-α-methylbutylamino)-5,6-dihydrofurano[2,3-*d*]pyrimidine (VIe).

A mixture of 7.82 g. (0.03 mole) of V and 9.48 g. (0.96 mole) of δ-diethylamino-α-methylbutylamine in a round bottom flask was heated with stirring in an oil bath at 220° for 30 minutes. After cooling to 150° the excess amine was removed at reduced pressure. The concentrated reaction mixture was dissolved in 150 ml. of hot 20% acetic acid, cooled, and the solution was made alkaline by addition of sodium hydroxide pellets and extracted with ether three times. The combined organic layers were washed with a small volume of water, dried (magnesium sulfate), the solvent removed, and the yellow oil distilled, giving 7.15 g. (62%) of product collected at 210-212°/0.5 mm.; λ max (neat), 3.02 μ (NH) and 6.25 μ (pyrimidine C=N). The NMR spectrum (deuteriochloroform), 8.29 δ (1H-S), 7.28 δ (5H-M), 4.22 δ (1H-S), 4.00 δ (1H-S). The region from 0.8 δ to 2.7 δ contains the chemical shifts of the protons of the 4-(δ-diethylamino-α-methylbutylamino) side chain and the 6,6-dimethyl groups which are difficult to decipher in the spectrum.

Anal. Calcd. for $C_{23}H_{34}N_4O$: C, 72.20; H, 8.96; N, 14.64. Found: C, 72.36; H, 9.09; N, 14.59.

4-Amino-5-(β,β-dimethyl-α-styryl)-6-chloropyrimidine (VIIa).

To 50 ml. of a saturated methanolic ammonia solution in a high pressure glass tube was added 2.61 g. (0.01 mole) of V. The tube was sealed, the mixture heated at 100-110° for 6 hours, cooled, and the contents transferred to a round bottom flask and concentrated to *ca.* one-fourth the initial volume. After cooling the final solution overnight, the colorless crystals were filtered and washed with a small volume of fresh methanol yielding 1.95 g. (75%) product, m.p. 192-194°. Recrystallization from 95% ethanol produced an analytically pure sample, m.p. 198.5-200°; λ max (potassium bromide), 2.98 μ (NH_2), 6.10 μ (1° NH) and 6.24 μ (C=C); λ max (ethanol), 280 mμ (sh) (ε = 6.250) and 235 mμ (ε = 19,800). The NMR spectrum (deuteriochloroform), 8.23 δ (1H-S), 7.24 δ (5H-S), 5.54 δ (2H-M), 1.89 δ (3H-S) and 1.71 δ (3H-S).

Anal. Calcd. for $C_{14}H_{14}ClN_3$: C, 64.73; H, 5.43; N, 16.18; Cl, 13.65. Found: C, 64.75; H, 5.61; N, 16.23; Cl, 13.57.

4-(δ-diethylamino-α-methylbutylamino)-5-(β,β-dimethyl-α-styryl)-6-chloropyrimidine (VIIb).

A mixture of 2.61 g. (0.01 mole) V and 1.90 g. (0.012 mole) of δ-diethylamino-α-methylbutylamine in a round bottom flask was heated with stirring in an oil bath at 170° for 2.5 hours. After cooling to 100° the reaction mixture was diluted with approximately 50 ml. of 20% acetic acid, cooled to room temperature, extracted twice with ether to remove the unreacted 4-chlorofurano[2,3-*d*]pyrimidine (0.5 g. of starting material recovered). The remaining aqueous acid solution was made alkaline by addition of sodium hydroxide pellets and extracted with ether 3 times. The combined organic extracts were washed with a small volume of water, dried (magnesium sulfate) and the filtrate condensed to a yellow oil. The oil was distilled, yielding 2.0 g. (62% based on consumed starting material) of product at 228-235°/0.6 mm.; λ max (neat), 2.90 μ (NH), 3.00 μ (NH) and 6.22 μ (C=C); λ max

(ethanol), 285 mμ (sh) (ε = 4,200) and 250 mμ (ε = 16,700).

Anal. Calcd. for $C_{23}H_{33}ClN_4$: C, 68.90; H, 8.29; N, 13.97. Found: C, 69.07; H, 8.65; N, 13.91.

4-Chloro-5-(β,β-dimethyl-α-styryl)-6-(γ-diethylaminopropylamino)-pyrimidine (VIIc).

(a) A round bottom flask containing 2.61 g. (0.01 mole) of V and 1.31 g. (0.01 mole) of γ-diethylaminopropylamine was immersed in an oil bath at 165° and stirred for 2 hours. The cooled reaction product was dissolved in 10% acetic acid and extracted once with ether to remove the unreacted starting material. The aqueous solution was made basic by addition of NaOH pellets and saturated with sodium chloride. The alkaline solution was then extracted with 3 portions of ether. The combined ether extracts were washed with a small volume of water, dried (magnesium sulfate), and the filtrate taken to dryness to give a pale yellow oil which was distilled, yielding 2.1 g. (56%) of product, 197-198°/0.1 mm.; λ max (neat), 3.0 μ (NH_2) and 6.22 μ (C=C); λ max (ethanol), 285 mμ (sh) (ε = 3,900) and 248 mμ (ε = 14,600). The NMR spectrum (deuteriochloroform), 8.25 δ (1H-S), 7.21 δ (5H-S), 5.91 δ (1H-M), 3.50 δ (2H-Q), 2.45 δ (4H-Q), 2.40 δ (2H-M), 1.92 δ (3H-S), 1.70 δ (3H-S), 1.62 δ (2H-M), and 0.92 δ (6H-T).

Anal. Calcd. for $C_{21}H_{29}ClN_4$: C, 67.65; H, 7.83; N, 15.02. Found: C, 67.73; H, 8.18; N, 14.77.

(b) To 10 ml. of dimethylformamide was added 1.304 g. (0.005 mole) of V and 0.65 g. (0.005 mole) of γ-diethylaminopropylamine. The resulting solution was stirred at reflux for 9 hours, poured into water and isolated as described above, yielding 0.9 g. (48%) of pale yellow oil. The infrared spectrum of the product was identical to that in procedure (a).

(c) To 25 ml. of 50% aqueous isopropyl alcohol was added 1.304 g. (0.005 mole) of V and 0.65 g. (0.005 mole) of γ-diethylaminopropylamine. The resulting solution was refluxed for 20 hours with stirring, concentrated to *ca.* 10 ml., poured into water and worked up as described above giving 0.8 g. (43%) of a yellow oil. Again the infrared spectrum was identical to that in procedure (a).

6-Chloro-5-(β,β-dimethyl-α-styryl)-3*H*-pyrimidine-4-one (VIII).

In a dry flask, 5.21 g. (0.02 mole) of V and 2.31 g. (0.02 mole) of pyridine hydrochloride was heated in an oil bath at 160-170° for 15 minutes during which time the mixture formed a clear melt. The resulting glassy mixture was cooled to *ca.* 80°, diluted with 50 ml. of water, made basic with potassium hydroxide, and extracted with 4 portions of ethyl acetate. The combined organic extracts were washed twice with water, dried (sodium sulfate), concentrated to about 50 ml. at reduced pressure and diluted with about 25 ml. of hexane to initiate crystallization. Chilling overnight afforded 4.0 g. (77%) of microcrystalline product, m.p. 176-180°. Recrystallization gave an analytical sample, m.p. 180-181°; λ max (potassium bromide) 2.92 (NH), 5.95 (C=O) and 6.29 μ (ar); NMR (deuteriochloroform), δ 7.85 (1H-S), 7.23 (5H-M), 1.82 (3H-S) and 1.73 (3H-S).

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.02; N, 10.75. Found: C, 64.71; H, 5.10; N, 10.91.

4,6-Dichloro-5-(β,β-dimethyl-α-styryl)pyrimidine (IX).

A mixture of 3.4 g. (0.013 mole) VIII, 30 ml. of phosphorus oxychloride and 1.5 ml. of acetic acid was heated at reflux for 75 minutes during which the reaction mixture darkened. The cooled reaction mixture was hydrolyzed in 300 g. of ice water for 15 minutes with stirring and made basic by slow addition of concentrated ammonium hydroxide. The resulting brown semisolid was extracted three times with chloroform, washed with water, dried (sodium sulfate), concentrated to a gummy mass at reduced pressure, dissolved in 50 ml. ethanol, treated with Norite, filtered, and 10-15 ml. water added to hot solution. Chilling yielded 2.3 g. of tan needles (65%), m.p. 72-73°; λ max (potassium bromide), 3.20-3.50 (CH), 6.67 μ (C-Cl) (15); NMR (deuteriochloroform), δ 8.66 (1H-S), 7.25 (5H-S), 1.91 (3H-S) and 1.67 (3H-S).

Anal. Calcd. for $C_{14}H_{12}Cl_2N_2$: C, 60.23; H, 4.33; N, 10.04. Found: C, 60.11; H, 4.46; N, 10.28.

4-Chloro-5-(β,β-dimethyl-α-styryl)-6-aminopyrimidine (VIIa) from IX.

A mixture of 1.8 g. (0.065 mole) IX and 65 ml. of ethanolic ammonia (*ca.* 1.5 *M*) was sealed in a high pressure bomb and heated for 6 hours at 110°. After cooling, the contents were transferred to a round bottom flask and concentrated at reduced pressure to dryness yielding a solid mass. The solid was redissolved in ethanol (40 ml.), decolorized with Norite, filtered, concentrated to 20 ml. and 3-5 ml. water added (to prevent ammonium chloride precipitation). The product separated as colorless plates. The yield was 1.45 g. (86%), m.p. 198.5-199.5°. The ir spectrum and melting point were identical to that of VIIa previously described.

6-Amino-5-(β,β-dimethyl-α-styryl)-3*H*-pyrimidine-4-one (X).

In a dry flask, 4.82 g. (0.02 mole) of VIa and 2.31 g. (0.02 mole) of pyridine hydrochloride were heated with stirring at 175-180° for about 20 minutes after which time the mixture had solidified into a pale yellow solid mass. (Initially the two reagents formed a homogeneous solution on heating). After cooling to 80°, water was added, and the mixture made basic by addition of potassium hydroxide pellets. The mixture was then extracted four times with ethyl acetate, washed twice with water, dried (sodium sulfate), concentrated to about 0.25 the initial volume and cooled. The resulting white crystalline product, 0.25 g. (5%), had a m.p. 290-291°. Recrystallization from 100 ml. ethyl acetate afforded an analytical sample, m.p. 292-293°: λ max (potassium bromide), 2.89 (OH), 3.05 (NH_2), 3.20 (NH_2) and 6.6 μ (C=O).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.70; H, 6.27; N, 17.42. Found: C, 69.86; H, 6.46; N, 17.54.

4,6-Diamino-5-(β,β-dimethyl-α-styryl)pyrimidine (XI).

A glass-lined steel bomb containing 100 ml. of ammonium hydroxide and 3.37 g. (0.013 mole) of VIIa was sealed and heated at 250° for 10 hours. The reaction mixture on cooling provided colorless crystals, collected by filtration, washed with 10 ml. of water, and dried in air, giving 2.5 g. (80%) of product. Recrystallization from 95% ethanol gave crystals m.p. 225-228°. A second recrystallization from methanol gave a sample with m.p. 228-231°; λ max (potassium bromide), 2.84 (NH), 3.01 (NH), 6.17 and 6.37 μ (pyrimidine (C=N).

Anal. Calcd. for $C_{14}H_{16}N_4$: C, 69.99; H, 6.70; N, 23.31. Found: C, 70.01; H, 6.97; N, 22.95.

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