Heterocycles. Part I. A New Route to the Synthesis of Substituted 2-Aminopyrimidines

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Heterocyclic aldehydes (A) reacted with alkyl aryl ketones (B) to give the corresponding 1,3-diaryl-2-propen-1-ones (Ia-l). Condensation of these chalcones with guanidine produced the corresponding 2-amino-4,6-diarylpyrimidines (IIa-l). The structure of all products was substantiated by chemical and spectroscopic methods.

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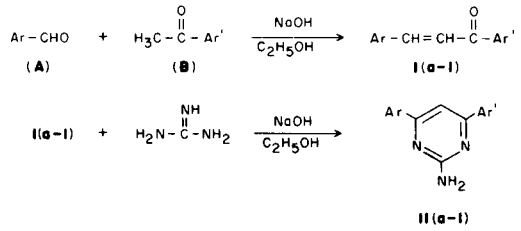
The present investigation describes a new route to the synthesis of pyrimidine derivatives of potential biological activity. Thus the different heterocyclic chalcones (Ia-l) were prepared and reacted with guanidine to produce the corresponding substituted pyrimidines (IIa-l). Some heterocyclic aldehydes were condensed with methyl-2-thienyl-, or methyl-2-furylketones to obtain the corresponding chalcones (Ia-f). The above aldehydes were also condensed with acetophenone or *p*-methoxyacetophenone to produce the chalcones (Ig-l) (*cf.*, Scheme 1).

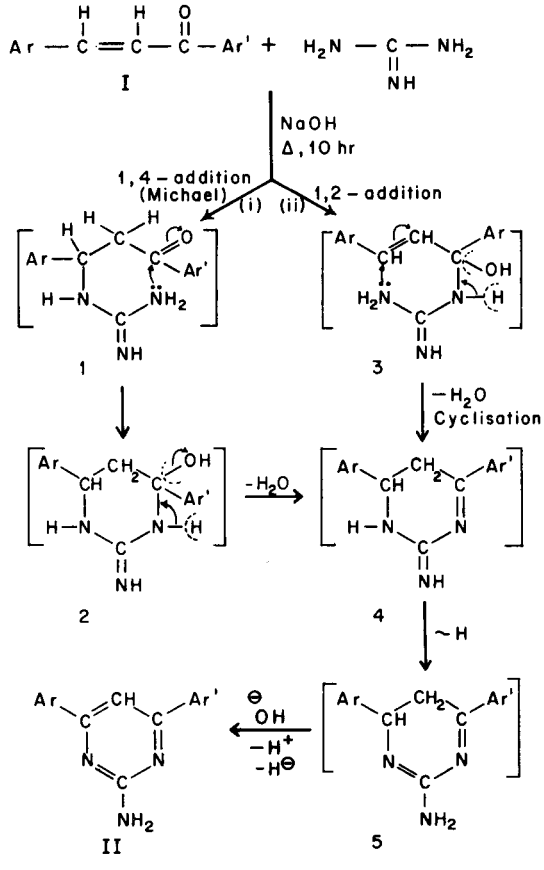


Scheme 1

Compound (I, II)	Ar	Ar'
a	C_4H_3S (thienyl)	C_4H_3S (thienyl)
b	C_4H_3O (furyl)	C_4H_3O (furyl)
c	C_4H_3S (thienyl)	C_4H_3O (furyl)
d	C_4H_3O (furyl)	C_4H_3S (thienyl)
e	C_4H_4N (pyrrolyl)	C_4H_3S (thienyl)
f	C_4H_4N (pyrrolyl)	C_4H_3O (furyl)
g	C_4H_3S (thienyl)	C_6H_5 (phenyl)
h	C_5H_5S (5-methylthienyl)	C_6H_5 (phenyl)
i	C_4H_3O (furyl)	C_6H_5 (phenyl)
j	C_4H_4N (pyrrolyl)	C_6H_5 (phenyl)
k	C_5H_6N (*N*-methylpyrrolyl)	C_6H_5 (phenyl)
l	C_4H_3S (thienyl)	C_7H_7O (*p*-methoxyphenyl)

The structure of these products was established from their spectroscopic and chemical analyses (*cf.*, Tables 1,4). Thus, their ir spectra show two bands in the ranges 1660-1642 cm^{-1} (νC=O) and 1610-1542 cm^{-1} (ν C=C), in addition to a third band for compounds (I,e,f,j) in the range 3260-3240 cm^{-1} (ν NH). The uv spectra show also two bands in the ranges 298-260 nm and 375-341 nm which can be ascribed to $\pi \rightarrow \pi^*$ transition. The nmr spectra lends further support for their structure and show signals characteristic for the olefinic and aromatic protons (*cf.*, Table 1).

The reaction of the above chalcones (Ia-l) with an alcoholic solution of guanidine carbonate containing aqueous sodium hydroxide solution, produced the corresponding 2-amino-4,6-diarylpyrimidines (IIa-l) (*cf.*, Scheme 2). This might proceed either by route (i) 1:4-addition or (ii) 1:2-addition of the guanidine to the chalcone, (*cf.*, Scheme 2) followed by cyclisation of the intermediates



Scheme 2

1 and **3** to give **4**. The latter undergoes proton shift and aromatization to yield the 2-aminopyrimidines (II). The Michael type addition (route i) seems to be more likely, by analogy to the reaction of nitrogen compounds with α,β-unsaturated carbonyl compounds (1,2,3).

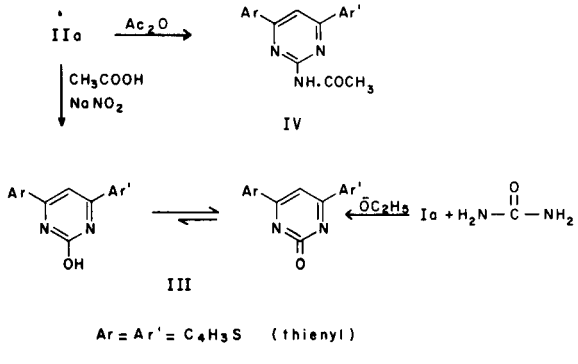
The structure of the products was established spectro-

Table I

The Infrared, Electronic, and Nuclear Magnetic Resonance Spectral Data of 1,3-Diaryl-2-propen-1-ones (Ia-l)

Compound	Infrared Spectra (Potassium Bromide)		Electronic Spectra (Ethanol)		NMR (Deuteriochloroform)	
	cm^{-1}	ν	λ max (nm)	ϵ	δ	Assignment
Ia	1650 (s)	C=O	285	7500	7.0-8.07	(m, 8, C=CH
	1575 (s)	C=C	350	23645		and Ar-H)
Ib	1660 (s)	C=O	279	8910	6.47-7.77	(m, 8, C=H
	1610 (s)	C=C	350	32310		and Ar-H)
Ic	1655 (s)	C=O	298	8530	6.53-8.13	(m, 8, C=H
	1600 (s)	C=C	352	23200		and Ar-H)
Id	1650 (s)	C=O	280	7330	6.57-7.9	(m, 8, C=H
	1590 (s)	C=C	350	30980		and Ar-H)
Ie	1642 (s)	C=O	272	8920	6.43-7.93	(m, 8, C=H
	1570 (s)	C=C	295 (sh)	7715		and Ar-H)
	1550 (s)		373	29480	5.20	(br, 1, N-H)
	3245 (m)	NH				
If	1642 (s)	C=O	285	4365	6.41-7.92	(m, 8, C=H
	1578 (s)		375	10390		and Ar-H)
	1550 (s)	C=C			5.1	(br, 1, N-H)
	3240	NH				
Ig	1652 (s)	C=O	275	20080	6.95-8.07	(m, 10, C=H
	1595 (s)		343	8250		and Ar-H)
	1585 (s)	C=C				
	1570 (s)					
Ih	1648 (s)	C=O	270	8445	6.6-8.0	(m, 9, C=H
	1595 (s)		354	21535		and Ar-H)
	1582 (s)	C=C			2.45	(s, 3, $-CH_3$)
	1575 (s)					
Ii	1660 (s)	C=O	260	6600	6.50-8.07	(m, 10, C=H
	1600 (s)	C=C	341	22580		and Ar-H)
Ij	1650 (s)	C=O	260	13710	6.70-8.07	(m, 10, C=H
	1582 (s)		370	26710		and Ar-H)
	1560 (s)	C=C			5.8	(br, 1, N-H)
	1542 (s)					
	3260 (m)	NH				
Ik	1640 (s)	C=O	260	9320	6.2-8.08	(m, 10, C=H
	1595 (s)		373	27225		and Ar-H)
	1580 (s)	C=C			3.07	(s, 3, $N-CH_3$)
	1560 (s)					
Il	1650 (s)	C=O	235	5820	6.8-8.03	(m, 9, C=H
	1600 (s)		290 (sh)	8760		and Ar-H)
	1585 (s)	C=C	345	25025	3.77	(s, 3, OCH_3)
	1570 (s)					

scopically and chemically. Thus, chemical reactions indicate that they have the aminopyridine structure II. This may be explained on the premise that, treatment of IIa with nitrous acid gave the 4,6-di-(2′-thienyl)-2-(1*H*)-pyrimidinone (III) (4), identical with the product obtained by the reaction between the chalcone (Ia) and urea in the presence of an alcoholic solution of sodium ethoxide (*cf.*, Scheme 3). The lactam form of compound III was inferred from its nmr and ir spectra. Thus its nmr spectrum shows no indication for the presence of enolic OH, but only a singlet at δ 3.3 (1H, -NH), and a multiplet centered at δ 7.70 (7, Ar-H). Its ir spectrum shows a strong band at 1660 cm^{-1} (ν C=O) and a broad band at 2860, 3098 cm^{-1} (ν NH bonded) (5). Acetylation of IIa with acetic anhydride gave the mono acetyl derivative IV (6). The ir spectrum of this compound shows a strong band at 1688 cm^{-1} (ν C=O) (7a) and two weak bands at 3398 and 3100 cm^{-1} (NH hydrogen bonded in the *trans*- and *cis*-forms, respectively) (7b) [chloroform solution of IV shows only one sharp band at



Scheme 3

Table 2

The Infrared, Electronic and Nuclear Magnetic Resonance Spectral Data of 2-Amino-4,6-diarylpyrimidines (IIa-l)

Compound	Infrared Spectra (Potassium Bromide)		Electronic Spectra (Ethanol)		NMR (Deuteriochloroform)	
	cm^{-1}	ν	λ max (nm)	ϵ	δ	Assignment
IIa	1640 (s)	C=N	227	8615	7.8	(s, 1, C=CH)
	1560 (s)	C=C	262	15735	7-7.5	(m, 6, Ar-H)
	3100 (m)		290	16110	5.43	(br, 2, NH_2)
	3220 (m)	NH_2	352	16860		
	3320 (m)					
IIb	1630 (s)	C=N	227	13630	7.43	(s, 1, C=CH)
	1600 (s)	C=C	248	13475	6.33-7.2	(m, 6, Ar-H)
	3180 (m)	NH_2	285	20925	5.40	(br, 2, NH_2)
	3300 (m)		350	17440		
IIc	1622 (s)	C=N	227	14650		
	1600 (s)	C=C	253 (sh)	16795	7.8	(s, 1, C=CH)
	1560 (s)		285	20725	6.53-7.63	(m, 6, Ar-H)
	3200 (m)		352	19655	5.33	(br, 2, NH_2)
	3320 (m)	NH_2				
	3410 (m)					
IId	1622 (s)	C=N	227	10410	7.8	(s, 1, C=CH)
	1600 (s)	C=C	253 (sh)	12250	6.6-7.6	(m, 6, Ar-H)
	1560 (s)		286	15820	5.4	(br, 2, NH_2)
	3200 (m)		352	13470		
	3320 (m)	NH_2				
	3400 (m)					
IIe	1635 (s)	C=N	225	8450	8.0	(s, 1, C=CH)
	1570 (s)	C=C	260	7760	6.76-7.7	(m, 6, Ar-H)
	1545 (s)		287	8335	6.4	(br, 1, NH)
	3080 (m)	NH_2	354	5710	5.17	(br, 2, NH_2)
	3240 (m)					
IIf	1650 (s)	C=N				
	1600 (m)	C=C				
	3120 (m)	NH_2				
	3350 (br)					
IIg	1640 (s)	C=N	222	13660	8.10	(s, 1, C=CH)
	1565 (s)	C=C	255	15000	7.1-7.8	(m, 8, Ar-H)
	1540		286	7120	5.26	(br, 2, NH_2)
	3210 (m)	NH_2	347	10075		
	3320 (m)					
IIh	1620 (s)	C=N	224	14070	8.10	(s, 1, C=CH)
	1565 (s)	C=C	253	15335	6.7-7.6	(m, 7, Ar-H)
	3200 (m)	NH_2	295	7215	5.15	(br, 2, NH_2)
	3315 (m)		350	12270	2.53	(s, 3, CH_3)
	4000 (m)					
IIi	1640 (s)	C=N	217	19215	8.13	(s, 1, C=CH)
	1595 (s)		255	19215	6.57-7.53	(m, 8, Ar-H)
	1585 (s)	C=C	280	14890	5.6	(br, 2, NH_2)
	1555 (s)		344	15210		
	3200 (m)	NH_2				
	3320 (m)					
IIj	1670 (m)	C=N	244	11010	7.93	(s, 1, C=CH)
					6.87-7.5	(m, 8, Ar-H)
	1575 (s)	C=C	350	6950	6.23	(br, 1, NH)
	3390 (br)	NH_2			5.16	(br, 2, NH_2)
IIk	1625 (s)	C=N	217	17365	8.0	(s, 1, C=CH)
	1580 (s)	C=C	247	16665	6.2-7.83	(m, 8, Ar-H)
	1570 (s)		292	8335	5.1	(br, 2, NH_2)
	3200 (m)		348	19730	4.0	(s, 3, N-CH_3)
	3320 (m)	NH_2				
	3480 (m)					
III	1640 (s)	C=N	228	12325	8.1	(s, 1, C=CH)
	1605	C=C	283	12170	6.87-7.9	(m, 7, Ar-H)
	3200 (m)	NH_2	348	9740	5.5	(br, 2, NH_2)
	3320 (m)				3.57	(s, 3, OCH_3)

Table 3

Electronic, Infrared and Nuclear Magnetic Resonance Spectral Data of III and IV

Compound	Infrared Spectra (Potassium Bromide)		Electronic Spectra (Ethanol)		NMR (Deuteriochloroform)	
	cm^{-1}	ν	λ max (nm)	ϵ	δ	Assignment
IIIa	1660 (s)	C=O	253-260	17350	7.2-8.2	(m, 7, Ar-H)
	1592 (s)	C=N	277	14785	3.3	(br, 1, N-H)
	2860 (m), 3095 (m)	NH	360	16090		
IVa	1688 (s)	C=O	235	20720	7.1-8.33	(m, 7, Ar-H)
	1665 (s)	C=N	270	21650	4.90	(br, 1, N-H)
	1583 (s)	C=C	287	20615	2.66	(s, 3, CH_3)
	3100 (m), 3398 (m)	NH	340, 353	26800, 25000		

Table 4

1,3-Diaryl-2-propen-1-ones (Ia-l)

Compound I	Yield (%)	Mp °C	Formula	Calcd. % C	H	N	S	Found % C	H	N	S
a	92	94-95	$C_{11}H_8OS_2$	60.0	3.63		29.10	60.10	3.70		29.27
b	85	86	$C_{11}H_8O_3$	70.21	4.25			70.27	4.28		
c	87	76	$C_{11}H_8O_2S$	64.70	3.92		15.68	64.75	3.95		15.85
d	85	76	$C_{11}H_8O_2S$	64.70	3.92		15.68	64.77	3.90		15.68
e	81	130	$C_{11}H_9NOS$	65.02	4.43	6.89	15.77	65.16	4.48	7.08	15.56
f	82	105	$C_{11}H_9NO_2$	70.58	4.80	7.48		70.40	4.57	7.83	
g	88	60	$C_{13}H_{10}OS$	72.89	4.67		14.95	72.70	4.69		15.14
h	90	75-77	$C_{14}H_{12}OS$	73.68	5.26		14.03	73.80	5.29		14.12
i	85	40	$C_{13}H_{10}O_2$	78.78	5.05			78.50	5.23		
j	80	136	$C_{13}H_{11}NO$	79.18	5.58	7.11		79.12	5.62	7.06	
k	83	76	$C_{14}H_{13}NO$	79.62	6.16	6.63		79.48	6.15	6.55	
l	93	100	$C_{14}H_{12}O_2S$	68.83	4.95		13.12	68.81	4.89		13.21

Table 5

2-Amino-4,6-diarylpyrimidines (IIa-l)

Compound II	Yield (%)	Mp °C	Formula	Calcd. % C	H	N	S	Found % C	H	N	S
a	81	162	$C_{12}H_9N_3S_2$	55.59	3.47	16.21	24.71	55.54	3.50	16.06	24.66
b	79	233-235	$C_{12}H_9N_3O_2$	63.43	3.96	18.50		63.52	3.95	18.48	
c	77	208-210	$C_{12}H_9N_3OS$	59.26	3.70	17.28	13.16	59.16	3.77	17.20	13.03
d	76	208-210	$C_{12}H_9N_3OS$	59.26	3.70	17.28	13.16	58.96	3.90	17.32	13.36
e	82	137	$C_{12}H_{10}N_4S$	59.50	4.13	23.14	13.22	59.48	4.36	23.16	13.30
f	75	170	$C_{12}H_{10}N_4O$	63.71	4.42	24.78		63.52	4.34	24.81	
g	79	114	$C_{14}H_{11}N_3S$	66.40	4.34	16.60	12.64	66.79	4.38	16.48	12.30
h	81	119	$C_{15}H_{13}N_3S$	67.41	4.86	15.73	11.98	67.75	5.15	15.50	11.83
i	82	148-150	$C_{14}H_{11}N_3O$	70.88	4.64	17.72		70.74	4.64	17.59	
j	71	164-166	$C_{14}H_{12}N_4$	71.18	5.08	23.72		71.26	5.28	23.53	
k	70	121-122	$C_{15}H_{14}N_4$	72.00	5.60	22.40		71.86	5.67	22.28	
l	78	171	$C_{15}H_{13}N_3OS$	63.60	4.59	14.84	11.30	63.43	4.71	14.74	11.22

3400 cm^{-1} (ν NH free) (7b)]. The nmr spectrum of IV shows signals which can be ascribed to ($COCH_3$) and (-CH=) protons, in addition to a multiplet fro aromatic and NH protons (*cf.*, Table 3). Further insight concerning the structure of IIa-l may be gleaned out from the consideration of their spectral data. Thus, their ir spectra (*cf.*, Table 2) show absorption bands in the region 1670-1620 cm^{-1} and 1605-1540, characteristic of the pyrimidine system (7c). In addition they show absorption bands which can be related to the amino group (free and bonded) (1). However, the ir spectrum of a dilute chloroform solution of IIa shows only two bands at 3522 and 3438 cm^{-1}, which correspond to asym- and sym-stretching frequencies of the free amino group. The nmr spectra of these compounds (*cf.*, Table 2) lend further support of the aminopyrimidine structure II. Thus, they show a broad signal in the range δ 5.2-5.4 (2, NH_2), which disappeared upon deuteration. The electronic

spectra of IIa-l show close resemblance, which reflects their structure analogy. The absorption bands in the ranges 295-280 nm, 262-244 nm and 354-344 nm can be ascribed to the ^{1}La and ^{1}Lb bands of the substituted 2-aminopyrimidines (1). The ms spectra of compounds IIa,b and l lend strong support to their postulated structure. They show the molecular ions (m/e 259, 227 and 283) as the base peaks respectively. This reflects the aromatic character of these compounds and supports the aminopyrimidine rather than the iminopyrimidine structure (*cf.*, Scheme 2).

EXPERIMENTAL

Melting points were done using a Bock-Monoscop M (thermal microscope), electronic and infrared spectra were measured on Cary 17 and Perkin-Elmer 580 B, respectively. The nmr spectra were run on Varian T60A. The ms were carried out using Varian MAT 311 A. Microanalyses were determined by A. Bernhardt, Microanalytical Laboratory, West Germany.

Preparation of 1,3-Diaryl-2-propen-1-ones (Chalcones) (Ia-l). General Procedure.

Quantitative amounts of the heterocyclic aldehyde (0.1 mole) and the aryl methyl ketone (0.1 mole) in ethanol (100 ml), were treated with sodium hydroxide solution (7 g/10 ml water). Addition of the base was carried out within 20 minutes. The mixture was stirred for 2 hours and the precipitated solid was filtered off and recrystallized from the proper solvent. Thus 1,3-di-(2′-thienyl)-2-propen-1-one (Ia), 1-(2′-thienyl)-3-(2′-furyl)-2-propen-1-one (Id) and 1-(2′-thienyl)-3-(2′-pyrrolyl)-2-propen-1-one (Ie) were obtained from the reaction of methyl 2-thienyl ketone with thiophene-2, furan-2-, and pyrrole-2-carboxaldehydes, respectively. On the other hand, 1,3-di-(2′-furyl)-2-propen-1-one (Ib), 1-(2′-furyl)-3-(2′-thienyl)-2-propen-1-one (Ic), and 1-(2′-furyl)-3-(2′-pyrrolyl)-2-propen-1-one (If), were produced by reacting methyl 2-furyl ketone and furan-2-, thiophene-2-, and pyrrole-2-carboxaldehydes, respectively. When acetophenone was allowed to react with thiophene-2-, 5-methylthiophene-2-, furan-2-, pyrrole-2- and *N*-methylpyrrole-2-carboxaldehydes, they gave 1-phenyl-3-(2′-thienyl)-(Ig), 1-phenyl-3-(5′-methyl-2′-thienyl)- (Ih), 1-phenyl-3-(2′-furyl)- (Ii), 1-phenyl-3-(2′-pyrrole)- (Ij) and 1-phenyl-3-(1′-methyl-2′-pyrrole)- (Ik) 2-propen-1-ones, respectively. The condensation of *p*-methoxyacetophenone and thiophene-2-carboxaldehyde gave 1-(*p*-methoxylphenyl)-3-(2′-thienyl)-2-propen-1-one (Il). The results are reported in Tables 1 and 4.

Reaction of 1,3-Diaryl-2-propen-1-ones (Ia-l) with Guanidine. General Procedure.

A mixture of the α,β-unsaturated ketone I (0.01 mole) and guanidine carbonate (0.01 mole) in ethyl alcohol (50 ml) was refluxed, while a solution of sodium hydroxide (5 mole) in water (5 ml) was added portion-wise during 2 hours. Refluxing was continued for a further 10 hours, and the reaction mixture was concentrated under reduced pressure, diluted with water (50 ml) and extracted with benzene. The products were crystallized from benzene to give 2-amino-4,6-di-(2′-thienyl)pyrimidine (IIa); 2-amino-4,6-di-(2′-furyl)pyrimidine (IIb); 2-amino-6-(4)-(2′-furyl)-4-(6)-(2′-thienyl)-pyrimidines (IIc,d); 2-amino-4-(2′-pyrrolyl)-6-(2′-thienyl)pyrimidine (IIe); 2-amino-6-(2′-furyl)-4-(2′-pyrrolyl)pyrimidine (IIf); 2-amino-6-phenyl-4-(2′-thienyl)pyrimidine (IIg); 2-amino-4-(5′-methyl-2′-thienyl)-6-phenylpyrimidine (IIh); 2-amino-4-(2′-furyl)-6-phenylpyrimidine (IIi); 2-amino-6-phenyl-4-(2′-pyrrolyl)pyrimidine (IIj); 2-amino-4-(1′-methyl-2′-pyrrolyl)-6-phenylpyrimidine (IIk) and 2-amino-6-(*p*-methoxyphenyl)-4-(2′-thienyl)pyrimidine (III).

Reaction of 2-Amino-4,6-di-(2′-thienyl)pyrimidine (IIa) with Nitrous Acid.

A solution of sodium nitrite (1.5 g) in water (10 ml) was added dropwise to a solution of the pyrimidine IIa (1.0 g) in glacial acetic acid (15 ml). The precipitated solid (0.9 g) was cyrstallized from acetone to give 4,6-di-(2′-thienyl)-2-(1*H*)pyrimidinone (III), as yellow crystals, mp 326-328°.

Anal. Calcd. for $C_{12}H_8N_2S_2$: C, 55.38; H, 3.07; N, 10.77; S, 24.61. Found: C, 55.21; H, 3.0; N, 10.82; S, 24.53.

An authentic sample of III was prepared by adding an alcoholic solution of urea (1.14 g in 10 ml of ethanol) to the solution of Ia (4.4 g) and sodium ethoxide (1.3 g) in absolute ethyl alcohol and the mixture refluxed for 4 hours, and kept at room temperature for 4 hours. The solvent was removed under reduced pressure and the residue dissolved in water (50 ml) and crystallized from acetone to give III in about 90% yield, mp and mixed mp 326-328°.

Acetylation of 2-Amino-4,6-di-(2′-thienyl)pyrimidine (IIa).

The pyrimidine IIa (1.0 g) was heated with acetic anhydride (3 ml) on a boiling water-bath for one hour. The product, precipitated on addition of cold 50% ethyl alcohol (15 ml), was crystallized from ethyl alcohol to give the corresponding 2-acetamido-4,6-di-(2′-thienyl)pyrimidine IV, as white crystals, mp 184-186°.

Anal. Calcd. for $C_{14}H_{11}N_3OS_2$: C, 55.81; H, 3.65; N, 13.95; S, 21.26. Found: C, 56.03; H, 3.69; N, 14.05; S, 21.34.

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