hr. The solvent was evapd, and the solid residue stirred with 10% NaOH soln and extd with $CHCl_3$. Following the usual work-up, a dark brown oil (7.2 g) was obtained. A sample of this oil was shown by gc analysis## to be a mixt of **4a** and **5a** (9:1 ratio). The main portion was chromatographed on neutral alumina (Woelm act. I) packed in C_6H_6. Elution with Et_2O gave an oil which was converted to 0.35 g of the fumarate salt of **5b**. Similarly, elution with Me_2CO–Et_2O and Me_2CO gave 3.5 g of **4a**·fumarate.

B. Basic Condition. (a) A soln of 0.058 mole of NaH (dispersed in oil) in 80 ml of anhyd DMSO under N_2 was stirred for 30 min. After 1.5 hr following the introduction 8.0 g (0.046 mole) of **3a**, a soln of 9.15 g (0.064 mole) of MeI in 20 ml of DMSO was slowly added with external cooling keeping the temp below 20°. After standing at 25° for 18 hr, the mixt was poured into crushed ice and extd with $CHCl_3$. The $CHCl_3$ soln was washed with H_2O to remove the DMSO and evapd to dryness leaving an oil. A sample was shown by gc analysis## to be a mixt of **4a** (24%), **5a** (56%), **6** (17%, retention time, 10.8 min) and an unidentified material (3%, retention time, 14.8 min). The oily mixt was chromatographed as described in the previous expt. From the C_6H_6 fractions, there was isolated 0.2 g of **6**. Compounds **4a** (3.6 g) and **5a** (0.8 g) were isolated as fumarates identical with that previously obtained.

(b) A suspension of 2.0 g (0.0116 mole) of **3a** and 0.5 g (0.0127 mole) of $NaNH_2$ in 60 ml of liq NH_3 was stirred for 30 min until dissolution occurred. A soln of 8.2 g (0.057 mole) of MeI in 20 ml of anhyd THF was added dropwise. After 5 hr, external cooling was discontinued, and the liq NH_3 evapd. The THF layer was decanted and the residue washed with H_2O, filtered, and dried to give 2.5 g of a solid. Recrystn from EtOH gave 0.6 g of **5a** (HI), mp 274–283° dec; nmr ($CDCl_3$–KOD) identical with that of **5a** (base) previously prepd. *Anal.* ($C_{11}H_{13}N_3O$·HI) C, H, N. The mother liquor was concd to give a ppt (mp 230–234°) which was suspended in MeOH and basified with 10% NaOH soln. On evapn of the MeOH and addn of H_2O to the residue, an oily material was pptd. Extn with Et_2O and evapn of Et_2O gave an oil, nmr spectrum ($CDCl_3$) identical with that of **4a** (base) previously prepd; mp of the fumarate also identical with that of **4a**·fumarate.

10-Methyl-2,3,5,10-tetrahydroimidazo[2,1-*b*]quinazoline-5-thione (4c). To a stirred soln of 1.0 g (0.005 mole) of **4b** in 40 ml of pyridine was added 4.2 g (0.0189 mole) of P_2S_5 and the mixt was refluxed for 5 hr. After evapg the solvent, the residue was triturated with hot H_2O to give **4c** (0.8 g after recrystn).

1-Acetyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (5b). A soln of 0.9 g (0.0052 mole) of **3a** in 25 ml of Ac_2O was heated on a steam bath for 15 min. It was concd, and the cryst ppt was filtered giving 0.93 g of **5b**.

1-Acetyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-5-one (5c). A soln of 1.5 g (0.008 mole) of **2a** in 25 ml of Ac_2O was warmed on a steam bath for 30 min. On cooling, the cryst product was filtered and washed with Et_2O giving 1.65 g of **5c**.

##Gas chromatography was performed on a Hewlett-Packard 5750 instrument with a 8 ft × 0.125 in. column, 3% OV-17 on 80–100 chromosorb W (HP), He 30 ml/min; initial column temp 150°, programmed 5°/min. Peaks were integrated automatically by an Infotronics CRS-100 instrument. Found retention time (min): **4a**, 8.3; **5a**, 10.1.

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Synthetic Antibacterials. 4.[1] Nitrofurylvinylpyrido[2,3-*d*]pyrimidine Derivatives

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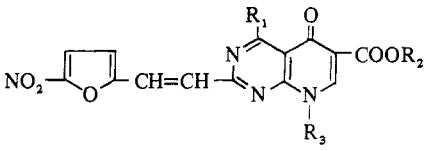
The synthesis of several 5-hydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido[2,3-*d*]pyrimidine-6-carboxylic acid derivatives and related compounds are discussed. Some members of the series display broad *in vitro* antibacterial activities against Gram-positive and Gram-negative organisms.

The attachment of a heterocyclic ring to the 2 position of the 5-nitrofuran ring frequently gives antimicrobial agents[2] and the introduction of a conjugated double bond between these rings often results in enhancing the *in vitro* activities.[3,4] In view of these facts we have synthesized several nitrofurylvinyl heterocycles[1,5,6] in an effort to obtain useful antibacterial agents and found that certain nitrofurylvinyl-1,8-naphthyridines (I)[6] possess outstanding activity against *Pseudomonas aeruginosa* as well as a variety of organisms. This paper is concerned with the synthesis and biological evaluation of 5-hydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido-[2,3-*d*]pyrimidine-6-carboxylic acid derivatives (II), which correspond to the analogous system of I mentioned above.

Chemistry. Treatment of ethyl 4-substituted-2-methyl-5-hydroxypyrido[2,3-*d*]pyrimidine-6-carboxylates (III)[7] with 5-nitrofurfural led to the formation of the respective nitrofurylvinylpyrido[2,3-*d*]pyrimidines (**1–6**) when the substituent in the 4 position was H, OH, OR, or PhO. The reaction was generally performed by heating the reactants in AcOH or Ac_2O. The free carboxylic acids of III do not condense with 5-nitrofurfural. Catalysts, such as concd H_2SO_4, which saponify III are therefore unsuited for the condensation reaction. Nitrofurylvinylpyrido[2,3-*d*]pyrimidines bearing amino substituents in the 4 position were prepared by heating the corresponding 4-alkoxy derivatives with amines such as $MeNH_2$, pyrrolidine, piperidine, or morpholine in DMF. This amination offers a convenient synthetic method of 4-aminonitrofurylvinylpyrido[2,3-*d*]pyrimidines (**7–10**), which could not be obtained by direct condensation from the corresponding 4-amino-5-hydroxy-2-methyl-

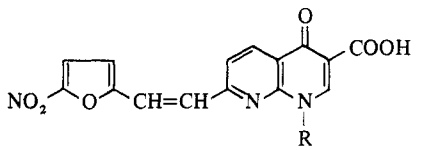
Table I. Nitrofurylvinylpyrido[2,3-*d*]pyrimidines



No.	R_1	R_2	R_3	Yield, %	Mp, °C	Recrystn solvent	Formula	Analysis
1	H	C_2H_5	H	52.6[a]	>320	AcOH	$C_{16}H_{12}N_4O_6$	C, H, N
2	OCH_3	C_2H_5	H	73.3[a]	282-286	AcOH	$C_{17}H_{14}N_4O_7$	C, H
3	OC_2H_5	C_2H_5	H	74.0[a]	254-256	AcOH	$C_{18}H_{16}N_4O_7$	C, H, N
4	OC_6H_5	C_2H_5	H	47.5[a]	274-278	AcOH	$C_{22}H_{16}N_4O_7$	C, H, N
5	OH	C_2H_5	H	76.0[a]	>320	DMF	$C_{16}H_{12}N_4O_7$	C, H, N
6	NHNHCHO	C_2H_5	H	29.4[a]	>320	EtOH	$C_{17}H_{14}N_6O_7$	C, H, N
7	$NHCH_3$	C_2H_5	H	84.4[b]	>300	DMF	$C_{17}H_{15}N_5O_6$	C, H, N
8	Pyrrolidyl	C_2H_5	H	50.0[b]	241-242	EtOAc	$C_{20}H_{19}N_5O_6$	C, H
9	Piperidyl	C_2H_5	H	54.0[b]	285	DMF	$C_{21}H_{21}N_5O_6$	C, H, N
10	Morpholinyl	C_2H_5	H	54.5[b]	278-280	DMF	$C_{20}H_{19}N_5O_7$	C, H, N
11	H	H	H	88.0[c]	>320	DMF	$C_{14}H_8N_4O_6$	C, H, N
12	OH	H	H	90.0[c]	>320	DMSO	$C_{14}H_8N_4O_7$	C, H, N
13	H	H	C_2H_5	30.0[d]	298-302	$CHCl_3$	$C_{16}H_{12}N_4O_6$	C, H, N
14	OH	H	C_2H_5	42.1[d]	>340	H_2O	$C_{16}H_{12}N_4O_7$	C, H, N
15	H	H	CH_3	68.5[d]	>320	DMF	$C_{15}H_{10}N_4O_6$	C, H
16	H	H	$CH_2CH_2N(C_2H_5)_2$	59.2[d]	275	EtOH	$C_{18}H_{21}N_5O_6$	C, H

[a]Prepared by the direct condensation of 2-methylpyrido[2,3-*d*]pyrimidines with 5-nitrofurfural. [b]Prepared by the amination of 4-ethoxy-2-nitrofurylvinylpyrido[2,3-*d*]pyrimidine (**3**) with appropriate amines. [c]Prepared by the hydrolysis of the corresponding 6-carboxylates. [d]Prepared by the alkylation of the corresponding 6-carboxylic acids.

Chart I



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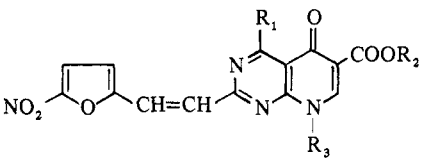
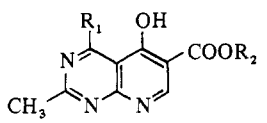


II

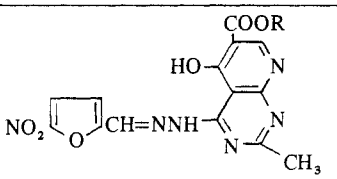


III, R_1 = H, OH, OAlk, OPh
IV, R_1 = $NHNH_2$

pyrido[2,3-*d*]pyrimidine-6-carboxylates and 5-nitrofurfural.

Ethyl 5-hydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido[2,3-*d*]-pyrimidine-6-carboxylate (**1**) was subjected to acid hydrolysis by refluxing in AcOH-concd HCl (9:1) to yield the corresponding 6-carboxylic acid (**11**). Other ethyl nitrofurylvinylpyrido[2,3-*d*]pyrimidine-6-carboxylates were similarly hydrolyzed, whereby all the 4 substituents were also hydrolyzed to give the same product, 4,5-dihydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido[2,3-*d*]pyrimidine-6-carboxylic acid (**12**). The latter compound could not be prepared by the condensation of 4,5-dihydroxy-2-methylpyrido[2,3-*d*]-pyrimidine-6-carboxylic acid with 5-nitrofurfural in a mixture of Ac_2O and AcOH or Ac_2O and CF_3COOH. Compounds **11** and **12** were refluxed with Et_2SO_4 and K_2CO_3 in DMF to give the corresponding 8-Et derivatives (**13**, **14**). Compound **11** was converted into the 8-Me derivative (**15**) with MeI and into the 8-diethylaminoethyl derivative (**16**) with diethylaminoethyl chloride in the presence of K_2CO_3 in EtOH (see Table I).

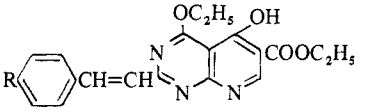
Table II. 4-[(5-Nitro-2-furyl)hydrazinomethine]pyrido[2,3-*d*]-pyrimidines



No.	R	Yield, %	Mp, °C	Recrystn solvent	Formula[a]
17	H	68.4	>320	DMF	$C_{14}H_{10}N_6O_6$
18	C_2H_5	30.0	255 dec	Me_2CO	$C_{16}H_{14}N_6O_6$

[a]*Anal.* C, H, N.

Table III. 2-Styrylpyrido[2,3-*d*]pyrimidines



No.	R	Yield, %	Mp, °C	Recrystn solvent	Formula[a]
19	Cl	34.9	255	DMF	$C_{20}H_{18}ClN_3O_4$
20	NO_2	50.8	265	DMF	$C_{20}H_{18}N_4O_6$

[a]*Anal.* C, H, N.

When 4-hydrazino-5-hydroxypyrido[2,3-*d*]pyrimidine-6-carboxylic acid derivatives (IV)[7] were treated with 5-nitrofurfural in Ac_2O-AcOH, the 4-[(5-nitro-2-furyl)hydrazinomethine]pyrido[2,3-*d*]pyrimidine derivatives (**17**, **18**) were formed (Table II). For comparison of their activities with those of the respective nitrofurylvinyl compounds, *p*-chloro- and *p*-nitrostyryl derivatives (**19**, **20**) were prepared by the condensation of ethyl 4-ethoxy-2-methylpyrido[2,3-*d*]-pyrimidine-6-carboxylate[7] with *p*-chloro- and *p*-nitrobenzaldehyde (Table III).

Table IV. *In Vitro* Antibacterial Activity

	Min inhib concn, μg/ml[a]															
No.	*Escherichia coli* Kaufmann O-1	*Klebsiella pneumoniae* ATCC 10031	*P. vulgaris*	*Ps. aeruginosa*	*Salmonella typhi* H 901w	*Staphylococcus enteritidis*	*S. flexneri* 2a 1675	*S. sonnei* II 37148	*Bacillus megatherium* 10778	*B. subtilis* ATCC 6633	*Micrococcus flavus* ATCC 10240	*Staph. aureus* FDA 209 P	*Staph. aureus* (Shimanishi)	*Staph. aureus* (Ōnuma)	*Mycobacterium* 607	*M. phlei*
1	0.19	1.56	>25	>25	1.56	0.78	0.39	0.39	0.39	0.19	1.56	0.39	0.19	0.19	>25	>25
2	3.13	6.25	>6.25	>6.25	6.25	3.13	1.56	1.56		0.78	1.56	0.19	0.04	0.04	6.25	6.25
3	>100	100	>100	>100	100		100	100		0.39	1.56	0.78	0.39	0.39	100	100
4	>25	>25	>25	>25	25	25	25	25		0.78	25	0.78	0.19	0.39	25	25
5	>50	>50	>50	>50	>50	>50	50	50	25	>50	>50	>50	>50	>50	>50	50
6	>25	>25	>25	>25	>25	25	25	>25	>25	> 25	25	12.5	25	25	>25	>25
7	6.25	6.25	>6.25	6.25	6.25	6.25	6.25	6.25	0.09	0.09	0.39	0.19	0.04	0.04	3.13	3.13
8	>100	12.5	>100	>100	100		100	100		1.56	3.13	0.78	0.39	0.39	12.5	12.5
9	25	25	>25	>25	25	12.5	25	25	0.39	0.39	0.13	0.39	0.09	0.09	12.5	12.5
10	25	12.5	>25	>25	25	6.25	25	25	3.13	3.13	3.13	3.13	3.13	3.13	>25	>25
11	25	6.25	>25	>25	25	3.13	6.25	25	3.13	3.13	3.13	3.13	3.13	3.13	>25	>25
12	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
13	3.13	1.56	12.5	12.5	6.25	3.13	3.13	3.13	0.09	0.09	0.39	0.39	0.09	0.09	12.5	12.5
14	>3.13	>3.13	>3.13	>3.13	>3.13	>3.13	>3.13	>3.13	>3.13	>3.13	>3.13	>3.13	>3.13	>3.13	3.13	3.13
15	6.25	25	25	25	6.25	3.13	3.13	6.25	1.56	0.78	1.56	1.56	1.56	0.78	12.5	6.25
16	12.5	25	25	25	12.5	3.13	6.25	12.5	3.13	1.56	3.13	3.13	1.56	1.56	12.5	6.25
17	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25
18	>25	25	>25	>25	25	12.5	25	25	12.5	6.25	25	3.13	6.25	3.13	25	25
19	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
20	>25	>25	>25	>25	>25	>25	>25	>25	6.25	6.25	6.25	12.5	3.13	3.13	50	50
b	6.25	6.25	>50	>50	12.5	6.25	3.13	12.5	3.13	3.13	>50	12.5	12.5	12.5	>50	>50
c	6.25	12.5	>50	>50	12.5	6.25	3.13	6.25	6.25	6.25	>25	12.5	12.5	12.5	>50	>50

[a]Minimum inhibitory concentration is the lowest concentration of the compound that prevents visible growth after 48 hr of incubation at 37°. [b]Nitrofurazone. [c]Nitrofurantoin.

Screening Results. The compounds were screened *in vitro* against a wide variety of bacteria (Table IV). Most of these compounds possess activity against both Gram-negative and Gram-positive organisms. Especially **1**, **2**, **7**, **13**, **15**, and **16** possess high antibacterial activity; the activity of **7**, **13**, **15**, and **16** against *Pseudomonas aeruginosa* and *Proteus vulgaris* is noteworthy. It is interesting to note that the parent 5-hydroxy-2-[2-(5-nitrofuryl)vinyl]pyrido-[2,3-*d*]pyrimidine-6-carboxylic acid (**11**) is less potent than the corresponding ester (**1**) or the 8-alkyl derivatives (**13**, **15**, **16**). The substitution of the nitrofurylvinyl group with the styryl group decreases the activity.

Experimental Section

Ethyl 5-Hydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido[2,3-*d*]-pyrimidine-6-carboxylates (1-6). An ethyl 5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylate and an equimolar amount of 5-nitrofurfural were refluxed in Ac_2O–AcOH (1:1) for several hours. The reaction mixt solubilized and then the product was pptd. After cooling, the separated crystals were collected by filtration, washed with AcOH and then Et_2O, and recrystd from AcOH or DMF to give a yellow powder.

Ethyl 5-Hydroxy-2-[2-(5-nitro-2-furyl)vinyl]-4-*sec*-aminopyrido-[2,3-*d*]pyrimidine-6-carboxylates (7-10). A mixt of ethyl 4-ethoxy-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylate and an equimolar amount of secondary amine ($MeNH_2$, pyrrolidine, piperidine, or morpholine) was heated in DMF at 120–130° for 10–90 min. After cooling, the product was removed by filtration and recrystd from a suitable solvent to give a yellow powder.

5-Hydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid (11). Ethyl 5-hydroxy-2-[2-(5-nitro-2-furyl)-vinyl]pyrido[2,3-*d*]pyrimidine-6-carboxylate (**1**) (0.45 g, 0.0013 mole) was refluxed for 2 hr in a mixt of AcOH (9 ml) and concd HCl (1 ml). The ppt was collected from the cooled solution, washed with H_2O, and recrystd from DMF to give yellow needles (0.37 g, 88%, mp >320°).

4,5-Dihydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid (12). A. A mixt of ethyl 4,5-dihydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido[2,3-*d*]pyrimidine-6-carboxylate (**5**) (0.40 g, 0.0011 mole), AcOH (27 ml), and concd HCl (3 ml) was refluxed for 1 hr. After cooling, the ppt was collected by filtration, washed with H_2O, and recrystd from DMSO to give a yellow powder (0.35 g, 90%, mp >320°).

B. A mixt of ethyl 4-methoxy-5-hydroxy-2-[2-(5-nitro-2-furyl)-vinyl]pyrido[2,3-*d*]pyrimidine-6-carboxylate (**2**) (0.45 g, 0.0012 mole), AcOH (9 ml), and concd HCl (1 ml) was refluxed for 1 hr. The precipitated crystals were removed from the cooled solution and recrystd from DMSO to give a yellow powder (0.35 g, 85.4%).

C. To a mixt of AcOH (10 ml) and concd HCl (3.3 ml) was added ethyl 4-methylamino-5-hydroxy-2-[2-(5-nitro-2-furyl)vinyl]-pyrido[2,3-*d*]pyrimidine-6-carboxylate (**7**) (1 g, 0.0026 mole) and the mixt was refluxed for 90 min. The precipitate was collected by filtration and recrystallized from DMF to give a yellow powder (0.53 g, 61.8%).

5,8-Dihydro-8-ethyl-2-[2-(5-nitro-2-furyl)vinyl]-5-oxopyrido-[2,3-*d*]pyrimidine-6-carboxylic Acid (13). A mixt of 5-hydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido[2,3-*d*]pyrimidine-6-carboxylic acid (**11**) (0.2 g, 0.0006 mole), Et_2SO_4 (0.09 g, 0.0006 mole), and K_2CO_3 (0.08 g) was heated in DMF (3 ml) at 130–150° for 2 hr. After cooling, the reaction mixt was diluted with Et_2O. The precipitated powder was collected and extracted with hot CH_3Cl. The extracts were evaporated and the residue was recrystd from $CHCl_3$ using charcoal to give yellow-brown needles (0.1 g, 30%, mp 298–302°).

5,8-Dihydro-8-ethyl-4-hydroxy-2-[2-(5-nitro-2-furyl)vinyl]-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic Acid (14). A mixt of 4,5-dihydroxy-2-[2-(5-nitro-2-furyl)vinyl]pyrido[2,3-*d*]pyrimidine-6-carboxylic acid (**12**) (0.53 g, 0.0015 mole), Et_2SO_4 (0.26 g, 0.0014 mole) and K_2CO_3 (0.5 g) was heated in DMF (10 ml) at 100° for 2 hr. After cooling, the product was removed by filtration and recrystd from H_2O to give yellow powder (0.24 g, 42.1%, mp >320°).

2-Methyl-5-hydroxy-4-[(5-nitro-2-furyl)hydrazinomethine]-pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid (17). To a mixt of 4-hydrazino-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylic acid (0.45 g, 0.0016 mole), Ac_2O (9 ml), and AcOH (9 ml) was added 5-nitrofurfural (0.25 g, 0.018 mole) and the mixt was refluxed at 140° for 2.5 hr. After cooling the product was collected by filtration, washed with AcOH, and recrystd from EtOH to give a yellow powder (0.2 g, 29.4%, mp >320°).

Ethyl 2-Methyl-5-hydroxy-4-[(5-nitro-2-furyl)hydrazinomethine]-pyrido[2,3-*d*]pyrimidine-6-carboxylate (18). To a mixt of ethyl 4-hydrazino-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylate (0.5 g, 0.0019 mole), Ac_2O (10 ml), and AcOH (10 ml) was added 5-nitrofurfural (0.25 g, 0.0018 mole) and the mixt was refluxed at 130° for 2 hr. The reaction mixt was diluted with H_2O, and the precipitate was collected by filtration and recrystd from Me_2CO to give a yellow powder (0.22 g, 30%, mp 255° dec).

Ethyl 4-Ethoxy-5-hydroxy-2-(*p*-nitrostyryl)pyrido[2,3-*d*]pyrimidine-6-carboxylate (20). A mixt of ethyl 4-ethoxy-5-hydroxy-2-methylpyrido[2,3-*d*]pyrimidine-6-carboxylate (0.8 g, 0.0029 mole), *p*-nitrobenzaldehyde (0.88 g, 0.0058 mole), Ac_2O (5 ml), and AcOH (5 ml) was refluxed for 3 hr. Yellow crystals were removed from the reaction mixt, washed with AcOH, and recrystd from DMF to give pale yellow crystals (0.6 g, 50.8%, mp 265°).

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