Folate Antagonists. 6. Synthesis and Antimalarial Effects of Fused 2,4-Diaminothieno[2,3-*d*]pyrimidines (1-3)

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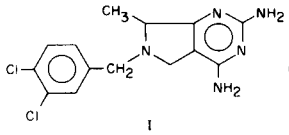
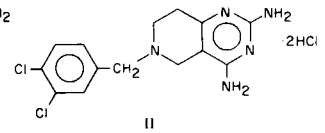
2,4-Diamino-5,7-dihydro-6*H*-thiopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidine, 2,4-diamino-9*H*-indeno[1',2':4,5]thieno[2,3-*d*]pyrimidine, 2,4-diamino-5*H*-indeno[2',1':4,5]thieno[2,3-*d*]pyrimidine, 9,11-diamino-5,6-dihydronaphtho[1',2':4,5]thieno[2,3-*d*]pyrimidine, 7,9-diamino-5,6-dihydronaphtho[2',1':4,5]thieno[2,3-*d*]pyrimidine, 2,4-diamino-7-benzyl-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidine, and various 2,4-diamino-5,6,7,8-tetrahydro-[1]benzothieno[2,3-*d*]pyrimidines were synthesized by cyclization of the requisite fused 2-aminothiophenene-3-carbonitriles utilizing chloroformamidine hydrochloride in diglyme. Several compounds exhibited strong inhibitory effects against *Streptococcus faecalis* (MGH-2), *Staphylococcus aureus* (UC-76), *Streptococcus faecium* (ATCC 8043), *Lactobacillus casei* (ATCC 7469), and *Pediococcus cerevisiae* (ATCC 8081) *in vitro*, and three compounds displayed antimalarial activity against *Plasmodium berghei* in mice and *P. falciparum* (Uganda I) *in vitro*.

Contemporary studies on folate antagonists in these laboratories have demonstrated that various 2,4-diamino-6-benzyl-5*H*-pyrrolo[3,4-*d*]pyrimidines (4) and 2,4-diamino-6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidines (5) exhibit significant antimalarial, antibacterial, and antimetabolite effects. When administered orally to mice infected with *Plasmodium berghei*, 2,4-diamino-6-(3,4-dichlorobenzyl)-7-methyl-5*H*-pyrrolo[3,4-*d*]pyrimidine (I) was equiactive with quinine hydrochloride (4),

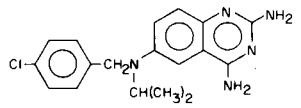


I

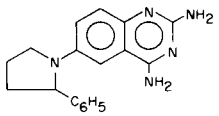


II

while 2,4-diamino-6-(3,4-dichlorobenzyl)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine dihydrochloride (II) was approximately twenty times as potent as this reference drug (5). The latter compound (II) was more active than the corresponding quinazoline antifolate 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline IIIa (Q = 7.9) (6,7) or the 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]-pyrido[2,3-*d*]pyrimidines IVa (Q = < 0.4) and IVb (Q = 6.2) (8), but was much less potent than other folate antagonists such as 2,4-diamino-6-[(3,4-dichlorobenzyl)nitrosamino]quinazoline (IIIb) (Q = 270) (9,10), 2,4-diamino-6-[(*p*-chlorobenzyl)isopropylamino]quinazoline (V) (Q = 1160) (11), and 2,4-diamino-6-(2-phenyl-1-pyrrolidinyl)quinazoline (VI) (Q = 210) (12,13).

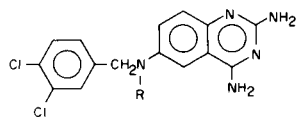


V

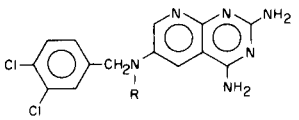


VI

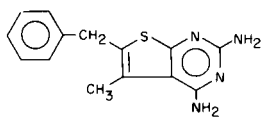
Certain 2,4-diaminothieno[2,3-*d*]pyrimidines can be viewed as bioisosteres of the antimalarial 2,4-diamino-5*H*-pyrrolo[3,4-*d*]pyrimidines (I), 2,4-diamino-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidines (II), 2,4-diaminopyrido-[2,3-*d*]pyrimidines (IV), and 2,4-diaminoquinazolines (III, V, VI) (1,4-13). Moreover, Roth (14) recently reported that 2,4-diamino-6-benzyl-5-methylthieno[2,3-*d*]pyrimidine (VII), a thienopyrimidine isostere of the potent



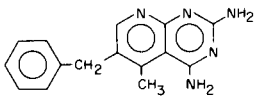
IIIa, R = H
b, R = NO



IVa, R = H
b, R = NO



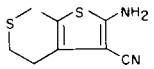
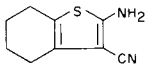
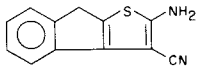
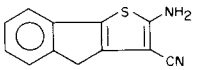
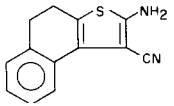
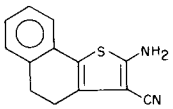
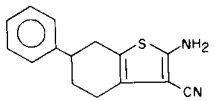
VII



VIII

TABLE I

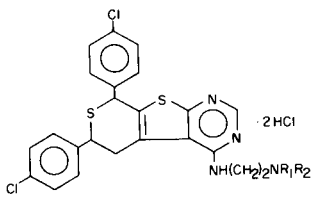
Fused 2-Aminothiophene-3-carbonitriles

Compound No.	Structure	M.p., °C	Yield purified, %	Purifcn solvent	Procedure	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1		206.5-209.5	61	MeCN	I	$C_8H_8N_2S_2$	48.95	48.84	4.11	4.14	14.28	14.26
2		142.5-145.5 (a)	61	*i*-PrOH	I	$C_9H_{10}N_2S$	60.64	60.64	5.66	5.79	15.72	15.90
3		151.5-155	25	EtOH	II	$C_{12}H_8N_2S$	67.89	67.96	3.80	4.11	13.20	13.28
4		239-241	41	EtOH	I	$C_{12}H_8N_2S$	67.89	68.06	3.80	4.08	13.20	13.31
5		165-168	48	C_6H_6	II	$C_{13}H_{10}N_2S$	69.00	69.00	4.45	4.61	12.38	12.33
6		194-196.5 (b)	40	EtOH	I	$C_{13}H_{10}N_2S$	69.00	69.16	4.45	4.48	12.38	12.49
7		177.5-180.5	63	EtOH	I	$C_{15}H_{14}N_2S$	70.83	70.87	5.55	5.72	11.02	11.20

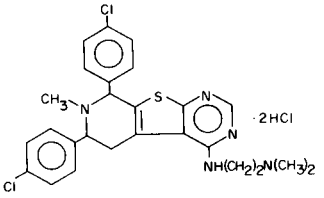
8	180-183	30	C_6H_6	II	$C_{15}H_{14}N_2S$	70.83	71.13	5.55	5.76	11.02	11.12
9	155-157.5 (c)	55	EtOH	I	$C_{15}H_{15}N_3S$	66.88	66.76	5.61	5.67	15.60	15.77

(a) Lit. (35) reports m.p. 147-148°. (b) Lit. (30) reports m.p. 195-197°. (c) Lit. (36) reports m.p. 149-152°.

antibacterial agent 2,4-diamino-6-benzyl-5-methylpyrido-[2,3-*d*]pyrimidine (VIII) (15), shows strong inhibitory effects against *Lactobacillus casei* and, like VIII, displays a favorable inhibition ratio against isolated dihydrofolate reductases from bacterial and mammalian sources (14). More distant relatives, such as the dihydrochloride salts of *cis* and *trans*-4-[[2-(dimethylamino)ethyl]amino]-6,8-bis(*p*-chlorophenyl)-5,6-dihydro-8*H*-thiopyrano[4′,3′:4,5]-thieno[2,3-*d*]pyrimidine (IXa) (16), the *cis* and *trans* diethyl analogs (IXb) (16), and *cis*-4-[[2-(dimethylamino)-ethyl]amino]-6,8-bis(*p*-chlorophenyl)-7-methyl-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine (X) (17), are reported to be active against drug-sensitive strains of *P. berghei* in mice when administered orally in daily



IX $N(R)_2$ = a, $N(CH_3)_2$; b, $N(C_2H_5)_2$



X

doses of 100 mg./kg. for 4 days. Moreover, compounds of type IXa and b are also active against primaquine-resistant strains of *P. berghei* (16), while X is effective against chloroquine-resistant lines (17). Since these compounds lack a six-membered ring incorporating the sequence $-N=C(NH_2)-N=C(NH_2)-$, which plays a key role in conferring optimal antiplasmodial effects among folate antagonists (6,18,19), it seems likely that they act by a different mechanism.

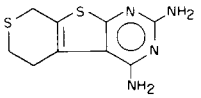
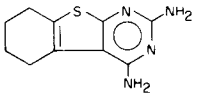
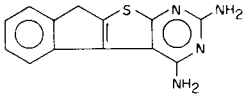
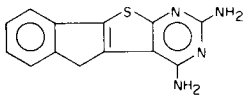
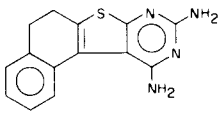
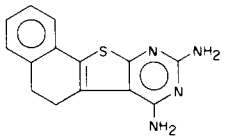
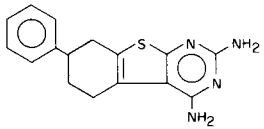
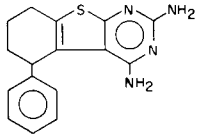
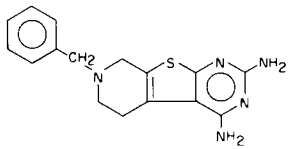
We have therefore synthesized several representative fused 2,4-diaminothieno[2,3-*d*]pyrimidine prototypes for antimalarial evaluation under the auspices of the Walter Reed Army Institute of Research (3). Rosowsky, Modest, and co-workers independently prepared a variety of 2,4-diaminothieno[2,3-*d*]pyrimidine derivatives, including several of the compounds (**11**, **15**, **16**, **19**) we had prepared earlier. Preliminary accounts of their studies have already appeared (20,21), and details of their work are being presented in separate communications (22-24).

Chemistry.

Interest in the chemistry of thieno[2,3-*d*]pyrimidines and fused thieno[2,3-*d*]pyrimidines has escalated since the first synthesis of a thieno[2,3-*d*]pyrimidine derivative was reported by Baker and co-workers in 1953 (25). A plethora of thieno[2,3-*d*]pyrimidines (14,25-30), [1]benzothieno[2,3-*d*]pyrimidines (27-33), naphtho[2′,1′:4,5]-thieno[2,3-*d*]pyrimidines (29,30), thiopyrano[4′,3′:4,5]-thieno[2,3-*d*]pyrimidines (16), and pyrido[4′,3′:4,5]-thieno[2,3-*d*]pyrimidines (17) has been prepared starting

TABLE II

Fused 2,4-Diaminothieno[2,3-*d*]pyrimidines

Compound No.	Structure	M.p., °C	Yield purified, %	Purifcn solvent	Procedure	Formula	Analyses (d) Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
10		278-282 dec.	11	AcOH	III	$C_9H_{10}N_4S_2$	45.36	45.29	4.23	4.40	23.51	23.40
11		241-242.5	30	EtOH	III	$C_{10}H_{12}N_4S$	54.51	54.35	5.42	5.21	25.43	25.38
12		>300	10	EtOH	III	$C_{13}H_{10}N_4S \cdot 0.6\ C_2H_6O \cdot 0.5\ H_2O$ (a)	58.61	58.70	5.06	4.86	19.26	19.24
13		310-312	8	DMF-H_2O, $C_6H_5CH_3$	III	$C_{13}H_{10}N_4S \cdot 0.07\ H_2O$ (b)	61.09	61.48	3.99	4.22	21.92	21.34
15		306-308	50	EtOH	IV	$C_{14}H_{12}N_4S$	62.66	62.91	4.51	4.67	20.88	20.81
16		257-260	16	EtOAc-isooctane	III	$C_{14}H_{12}N_4S \cdot 0.15\ H_2O$ (c)	62.04	62.37	4.57	4.70	20.68	20.32
17		267-269	67	DMF-dil NaOH	III	$C_{16}H_{16}N_4S$	64.84	65.04	5.42	5.54	18.91	18.97
18		274-277	62	DMF-dil NH_4OH	III	$C_{16}H_{16}N_4S$	64.84	64.45	5.42	5.53	18.91	18.92
19		178-180.5	9	EtOAc	III	$C_{16}H_{17}N_5S$	61.71	61.14	5.50	5.61	22.49	22.12

(a) H_2O: calcd., 3.10; found, 3.02. (b) H_2O: calcd., 0.49; found, 0.21. (c) H_2O: calcd., 0.99; found, 0.95. (d) Water analyses by the Karl Fischer Method.

from either thiophene or pyrimidine fragments. However, only one fused 2,4-diaminothieno[2,3-*d*]pyrimidine has been reported, namely 2,4-diamino-5,6,7,8-tetrahydro-[1]benzothieno[2,3-*d*]pyrimidine (**11**) (27). This compound was obtained by the condensation of 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile with cyanamide and pyridine hydrochloride.

In the present work, a majority of the intermediate fused 2-aminothiophene-3-carbonitriles (XI) (**1**, **2**, **4**, **6**, **7**, **9**, Table I) were prepared directly from the corresponding ketones by treatment with sulfur and malononitrile in the presence of morpholine (40-63% yield, procedure I), a modification of the Willgerodt-Kindler reaction of ketones with sulfur and ammonia (34,35). In those instances where the single step procedure was unsatisfactory (**3**, **5**, **8**, Table I), a stepwise process was utilized wherein the Knoevenagel-Cope intermediate formed from the ketone and malononitrile was first isolated, and was then treated with sulfur and morpholine or triethylamine (25-48% yield, procedure II). 2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carbonitrile (**9**) and related compounds have recently been synthesized by this overall procedure, and are reported to have analgetic and antiinflammatory activity (36,37).

Cyclization of the intermediate 2-aminothiophene-3-carbonitriles (XI) to the desired fused 2,4-diaminothieno-[2,3-*d*]pyrimidines (Chart I, Table II) was accomplished utilizing chloroformamidine hydrochloride (38) in diglyme (procedure III), a method developed earlier for the conversion of 2-aminobenzonitriles to 2,4-diamino-6-(heterocyclic)quinazolines (12,13) and 2,4-diamino-6-(aryloxy and aralkoxy)quinazolines (1). From compounds **1-4** and **6-9** (Table I) were thus obtained 2,4-diamino-5,7-dihydro-6*H*-thiopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidine (**10**) (11%), 2,4-diamino-5,6,7,8-tetrahydro-[1]benzothieno[2,3-*d*]pyrimidine (**11**) (30%), 2,4-diamino-9*H*-indeno-[1',2':4,5]thieno[2,3-*d*]pyrimidine (**12**) (10%), 2,4-diamino-5*H*-indeno[2',1':4,5]thieno[2,3-*d*]pyrimidine (**13**) (8%), 7,9-diamino-5,6-dihydronaphtho[2',1':4,5]thieno-[2,3-*d*]pyrimidine (**16**) (16%), 2,4-diamino-5,6,7,8-tetrahydro-7-phenyl-[1]benzothieno[2,3-*d*]pyrimidine (**17**) (67%), 2,4-diamino-5,6,7,8-tetrahydro-5-phenyl-[1]benzothieno[2,3-*d*]pyrimidine (**18**) (62%), and 2,4-diamino-7-benzyl-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]-pyrimidine (**19**) (9%). In the case of 2-amino-4,5-dihydronaphtho[2,1-*b*]thiophene-1-carbonitrile (**5**), this condensation afforded the uncyclized intermediate (1-cyano-4,5-dihydronaphtho[2,1-*b*]thien-2-yl)guanidine (**14**) (procedure IV). Ring-closure to **15** was readily accomplished by heating **14** in dimethylformamide (86%, 50% overall).

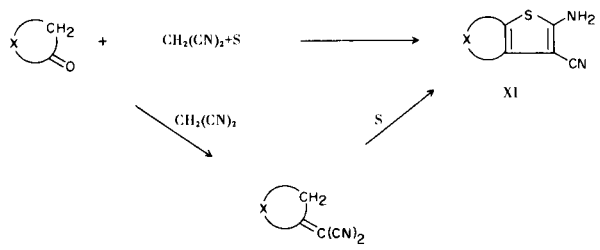
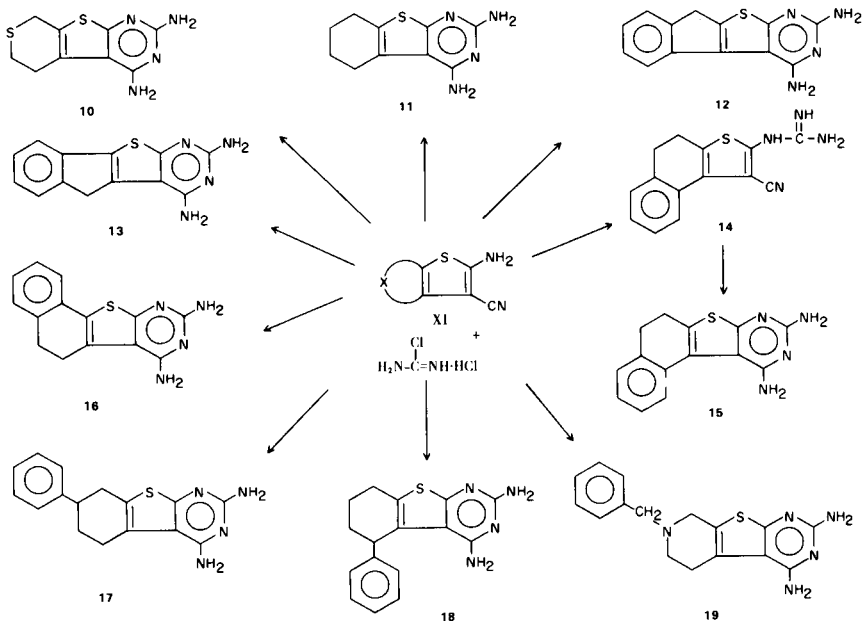


CHART I



The naphtho[1′,2′:4,5]thieno[2,3-*d*]pyrimidine (**15**), indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidine (**12**), and indeno-[2′,1′:4,5]thieno[2,3-*d*]pyrimidine (**13**) ring systems are unknown based on a search of *Chemical Abstracts* and "The Ring Index" (39), and thus appear to represent novel heterocyclic types.

Biological Results.

Antimalarial Effects.

The fused 2,4-diaminothieno[2,3-*d*]pyrimidines described in the present communication, together with the condensed 2-aminothiophene-3-carbonitriles employed as synthetic intermediates, were evaluated for antimalarial activity utilizing *P. berghei* in mice, *P. gallinaceum* in chicks, and *P. falciparum in vitro*. The thieno[2,3-*d*]-pyrimidines (**10-13**, **15-19**, Table II) and the 2-aminothiophene-3-carbonitriles [**1-5**, **7-9** (Table I), and **14**] were administered subcutaneously to mice infected with a normal drug-sensitive strain of *P. berghei* (40,41) in single doses ranging from 20 to 640 mg./kg. 2,4-Diamino-5,7-dihydro-6*H*-thiopyrano[4′,3′:4,5]thieno[2,3-*d*]pyrimidine (**10**) and 2,4-diamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**11**) each increased the survival time of mice 2.9 days at a dose of 640 mg./kg. This suggests that they may have slight antimalarial activity, although the significance of these data is borderline. Compounds **12**, **13**, **15**, **17**, and **18** were tolerated well at the highest levels tested (160-640 mg./kg.), but were ineffective against *P. berghei*. The thienopyrimidines **16** and **19** were toxic for mice at doses of 160 mg./kg. and 80 mg./kg., respectively, and likewise showed no activity against the plasmodia. Although the intermediate 2-aminothiophene-3-carbonitriles (**1-5**, **7-9**, Table I) were tolerated well by mice at 640 mg./kg., no antimalarial activity was observed. The guanidine derivative (**14**) was toxic at 320 mg./kg. and lacked antimalarial effects.

Three of the carbocyclic 2,4-diaminothieno[2,3-*d*]-pyrimidines (**10**,**13**,**16**) and the intermediate 2-aminothiophene-3-carbonitriles (**3**,**5**) were also tested against *P. gallinaceum* infections in white Leghorn cockerels (1,40,41). None exhibited significant anitmalarial effects when given in single intravenous or subcutaneous doses ranging from 10-320 mg./kg., but each was tolerated well.

In contradistinction, 2,4-diamino-7-benzyl-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine (**19**) exhibited high activity against the drug-sensitive Uganda I strain of *P. falciparum in vitro* (42-44). When the parasites were incubated with **19** at drug concentrations ranging from 25 to 5,000 μg./ml., > 90% of the parasites, relative to the control sample, were unable to mature to schizonts. Against the drug-resistant Vietnam Marks strain, however, compound **19** was virtually ineffective over the same concentration range.

Antibacterial Activity.

Three of the condensed 2,4-diaminothieno[2,3-*d*]-pyrimidines (**11**, **16**, **17**) were tested *in vitro* against a spectrum of pathogenic bacteria including *Streptococcus faecalis* (MGH-2), sensitive (UC-76) and drug-resistant (S18713) *Staphylococcus aureus*, *Pseudomonas aeruginosa* (28), *Escherichia coli* (Vogel), and *Shigella sonnei* (C-10). A modification of the gradient plate procedure of Szybalski (45) and Webb and Washington (46) was employed throughout (13). 7,9-Diamino-5,6-dihydronaphtho[2′,1′:4,5]thieno[2,3-*d*]pyrimidine (**16**) produced 50% inhibition of *S. faecalis* (MGH-2) at 1.0 μg./ml. and 2,4-diamino-5,6,7,8-tetrahydro-7-phenyl-[1]benzothieno-[2,3-*d*]pyrimidine (**17**) inhibited *S. aureus* (UC-76) at 25 μg./ml., but both were inactive against the other bacteria at 25 μg./ml. Compound **11** was inactive against all test organisms at 25 μg./ml.

Antimetabolite Effects.

Three of the thieno[2,3-*d*]pyrimidines (**11**, **12**, **18**) were evaluated for their inhibitory effects on *Streptococcus faecium* (*S. faecalis* ATCC 8043), *Lactobacillus casei* ATCC 7469, and *Pediococcus cerevisiae* ATCC 8081 (47). 2,4-Diamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**11**) and 2,4-diamino-9*H*-indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidine (**12**) produced 50% inhibition of *S. faecium* at 30 and 37 ng./ml., *L. casei* at 290 and 11,800 ng./ml., and *P. cerevisiae* at 300 and 185 ng./ml., respectively. Compound **18** was inactive against all three organisms at a concentration of 100,000 ng./ml. Obviously the relative inhibitory activity of the thieno[2,3-*d*]-pyrimidines against these organisms does not afford a reliable basis for predicting the magnitude of antimalarial effects.

EXPERIMENTAL (48)

Fused 2-Aminothiophene-3-carbonitriles (XI) (**1-9**, Table I). Procedure I.

To a stirred suspension of 8.7 g. (0.05 mole) of 4-phenylcyclohexanone (49), 3.3 g. (0.05 mole) of malononitrile, and 1.6 g. (0.05 mole) of sulfur in 30 ml. of ethanol was added gradually 5 ml. of morpholine. Heat was evolved, and the temperature rose to 43°. Partial solution occurred, but before complete solution was attained a copious precipitate formed. The reaction mixture was stirred at room temperature for 3 hours and was filtered. The product was collected and recrystallized from 180 ml. of ethanol to give 8.0 g. (63%) of 2-amino-4,5,6,7-tetrahydro-6-phenylbenzo[*b*]thiophene-3-carbonitrile (**7**) as shiny plates, m.p. 177.5-180.5°.

Procedure II.

A suspension of 54.9 g. (0.28 mole) of 3,4-dihydro-$\Delta^1(2H),\alpha$-naphthalenemalononitrile (50) and 9.1 g. of sulfur in 500 ml. of ethanol containing 25 ml. of morpholine was stirred and heated under reflux for 12 hours. The reaction mixture was allowed

to stand at room temperature for 3 days. The solid that separated was collected (37.4 g.) and recrystallized from 500 ml. of benzene to give 30.4 g. (48%) of 2-amino-4,5-dihydronaphtho[2,1-*b*]-thiophene-1-carbonitrile (**5**) as beige crystals, m.p. 165-168°.

Fused 2,4-Diaminothieno[2,3-*d*]pyrimidines (**10-13**, **15-19**, Table II). Procedure III.

A mixture of 5.8 g. (0.023 mole) of 2-amino-4,5,6,7-tetrahydro-6-phenylbenzo[*b*]thiophene-3-carbonitrile (**7**) and 2.9 g. (0.025 mole) of chloroformamidine hydrochloride (38) in 12 ml. of diglyme was stirred and heated in an oil bath at 150-155°. Hydrogen chloride was evolved and a clear solution formed. After 0.75 hour, a new solid had precipitated and the mixture was cooled. The yellow solid was collected, washed successively with diglyme and ether, and air dried. The solid was suspended in dilute sodium hydroxide, stirred at room temperature for 0.5 hour, collected, washed with water, and dried. Crystallization from dimethylformamide containing dilute sodium hydroxide solution gave yellow crystals of 2,4-diamino-5,6,7,8-tetrahydro-7-phenyl-[1]benzothieno[2,3-*d*]pyrimidine (**17**). After drying *in vacuo* at 50° for 18 hours, the product weighed 4.5 g. (67%), m.p. 267-269°.

Procedure IV.

A suspension of 5.9 g. (0.026 mole) of 2-amino-4,5-dihydronaphtho[2,1-*b*]thiophene-1-carbonitrile (**5**) in 15 ml. of diglyme was heated in an oil bath to 130° to effect solution. Chloroformamidine hydrochloride (38) (3.3 g., 0.029 mole) was added and the bath temperature was increased to 155°. After several minutes a clear orange solution formed, hydrogen chloride was evolved, and a yellow solid formed. After 10 minutes, the reaction was cooled and the solid was collected, washed successively with diglyme and ethyl acetate, and dried in the air (5.4 g.). The solid was dissolved in 200 ml. of hot 95% ethanol containing 2 ml. of concentrated ammonium hydroxide, and the mixture was diluted with 350 ml. of water and chilled. The solid that formed was collected, washed with water, and dried *in vacuo* at 50° to give 4.0 g. (58%) of (1-cyano-4,5-dihydronaphtho[2,1-*b*]thien-2-yl)guanidine (**14**) as off-white crystals, m.p. 304-307° with prior sintering.

Anal. Calcd. for $C_{14}H_{12}N_4S$: C, 62.66; H, 4.51; N, 20.88. Found: C, 62.54; H, 4.57; N, 21.14.

The ir spectrum showed a strong nitrile band at 2210 cm^{-1}.

A solution of 3.5 g. (0.013 mole) of (1-cyano-4,5-dihydronaphtho[2,1-*b*]thien-2-yl)guanidine (**14**) in 7.5 ml. of dimethylformamide was heated under reflux for 3 hours. The mixture was cooled, filtered, and the solid was washed with ethanol and air dried. The desired 9,11-diamino-5,6-dihydronaphtho[1',2':4,5]-thiano[2,3-*d*]pyrimidine (**15**) (3.0 g., 86%) (50% overall) was obtained as beige needles, m.p. 306-308°.

$\Delta^{1,\alpha}$-Indanmalononitrile.

A solution of 66.0 g. (0.5 mole) of 1-indanone and 33.0 g. (0.5 mole) of malononitrile in 200 ml. of benzene containing 4.0 g. of ammonium acetate and 12 ml. of acetic acid was heated under reflux under a Dean Stark water separator for 9 hours. A total of 13.5 ml. of water was collected. The mixture was cooled and filtered. The solid (70.7 g.) was recrystallized from benzene to give 50.3 g. (56%) of product. An analytical sample was prepared by recrystallization from benzene, m.p. 146-150°.

Anal. Calcd. for $C_{12}H_8N_2$: C, 79.98; H, 4.47; N, 15.55. Found: C, 79.89; H, 4.76; N, 15.49.

2-Phenyl-$\Delta^{1,\alpha}$-cyclohexanemalononitrile.

A solution of 41.0 g. (0.235 mole) of 2-phenylcyclohexanone and 15.5 g. (0.235 mole) of malononitrile in 200 ml. of benzene containing 1.9 g. of ammonium acetate and 5.7 ml. of acetic acid was heated under reflux utilizing a Dean Stark water separator. After 4 hours, 7.0 ml. of water had collected. The solvent was removed *in vacuo* and the residual syrup was suspended in water and made basic with aqueous sodium carbonate. The oil was induced to solidify by scratching, and the solid was collected, washed with water and dried in air to give 49.0 g. of crude product. Recrystallization from 200 ml. of 2-propanol yielded 40.2 g. (77%) of product, m.p. 63-67.5°. A small sample was recrystallized again for analysis, m.p. 65-69°.

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.92; H, 6.48; N, 12.68.

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