

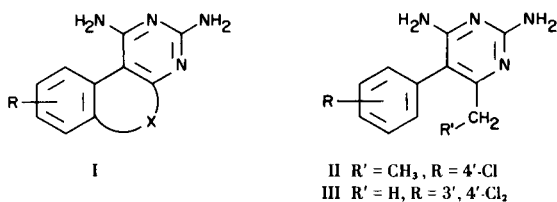
Synthesis of 2,4-Diamino-9*H*-indeno[2,1-*d*]pyrimidines (1)

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As part of a search for new antifolic, antimalarial, and antitumor agents, a series of 2,4-diamino-9*H*-indeno[2,1-*d*]pyrimidines was prepared by condensation of guanidine with substituted 2-alkoxy-3-cyano-1*H*-indenes. Base-catalyzed cyclization of 1,2-bis(cyanomethyl)benzenes afforded 2-amino-3-cyano-1*H*-indenes, which were converted into 3-cyano-2-methoxy-1*H*-indenes by acid hydrolysis and treatment of the resultant 1-cyano-2-indanones with diazomethane. Alternatively, 2-amino-3-cyano-1*H*-indenes could be transformed directly into 2-ethoxy-3-cyano-1*H*-indenes by reaction with ethanol and sulfuric acid. The 2,4-diamino-9*H*-indeno[2,1-*d*]pyrimidines represent a new type of planar, tricyclic pyrimethamine analog, in which free rotation of the phenyl and pyrimidine rings is prevented by means of a methylene bridge.

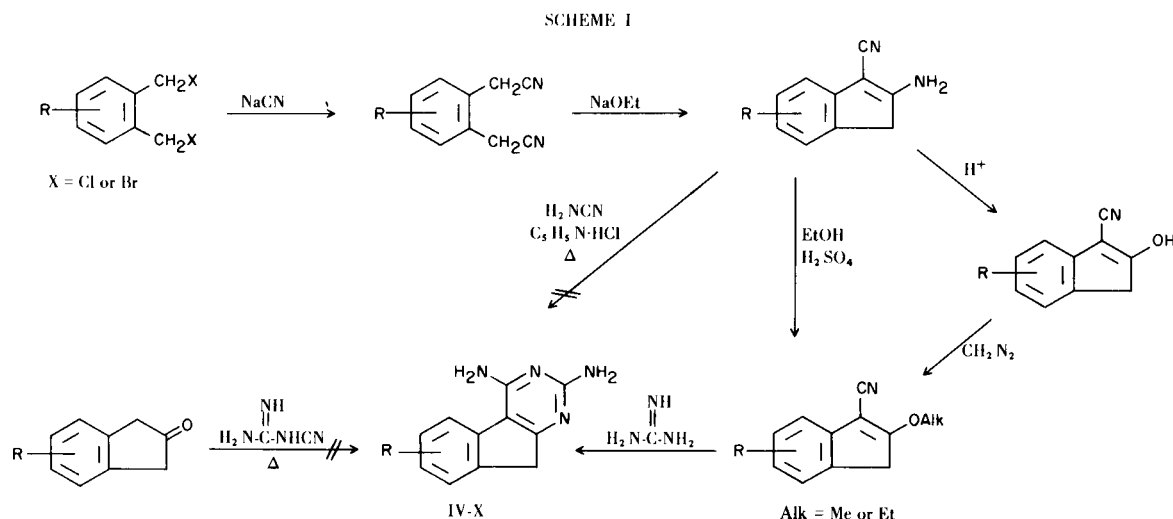
As part of a larger chemical and biological program involving polycyclic 2,4-diaminopyrimidines (2), we recently reported the synthesis (3-5) and growth-inhibitory properties (6) of 1,3-diaminobenzo[*f*]quinazolines (I, X = -CH=CH-) and 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines (I, X = -CH<sub>2</sub>CH<sub>2</sub>-). These tricyclic systems are of considerable interest as structural analogs of pyrimethamine (II), a well-known antifolic agent which has been used clinically for a number of years in the treatment of malaria (7). Additional interest in these analogs was provided by the experimental antitumor activity reported for the closely related 2,4-diamino-5-(3',4'-dichlorophenyl)-6-methylpyrimidine (III) (8).



The biological rationale underlying this approach to analog design has been discussed previously (9). In essence, it is proposed that the biological activity of 2,4-diaminopyrimidines and other drugs of the pyrimethamine type may depend upon their ability to assume a coplanar configuration on the surface of the target enzyme dihydrofolate reductase (10). The substantial growth-inhibitory activity

of 1,3-diaminobenzo[*f*]quinazolines and their 5,6-dihydro derivatives in various experimental test systems (6) encouraged us to extend the investigation of tricyclic pyrimethamine analogs to other compounds having the general structure I. In this paper, we should like to report the synthesis of a series of hitherto unknown 2,4-diamino-9*H*-indeno[2,1-*d*]pyrimidines (I, X = -CH<sub>2</sub>-) from 2-alkoxy-3-cyano-1*H*-indenes and guanidine. The indeno[2,1-*d*]pyrimidine ring system (11) was first cited in two Belgian patents (12), which reported the condensation of formamide with 2-amino- and 2-acylamino-3-cyano-1*H*-indenes at elevated temperatures. The resultant 9-cyano- and 2-alkyl-9-cyano-1*H*-indeno[2,1-*d*]pyrimidines, and some of their 1- and 3-alkyl derivatives, were tested for pharmacological activity (13). To our knowledge, these are the only references to this ring system up to the present time.

Initial attempts to prepare 2,4-diamino-9*H*-indeno[2,1-*d*]pyrimidine (IV) *via* direct condensation of 2-indanone and cyanoguanidine (14) were unsuccessful, both under fusion conditions and in high-boiling solvents. The only identifiable product recovered from the reaction mixture was the dimer, 1-(2-indanylidene)-2-indanone. This result was not unexpected, since it has been known for many years that 2-indanone undergoes self-condensation readily upon being heated or upon treatment with acid or base (15). Condensation of cyanoguanidine with the morpholine or hexamethylenimine enamine of 2-indanone in dimethylformamide at various temperatures was also attempted. This technique had been used



previously to prepare condensed 2,4-diaminopyrimidines at temperatures below those normally required for fusion reactions (16). The enamines failed to react with cyanoguanidine, being recovered unchanged even after prolonged refluxing in *N,N*-diethylformamide (b.p. 178°).

Compound IV was prepared successfully *via* the longer, more conventional route shown in Scheme 1. 1,2-Bis(cyanomethyl)benzene was cyclized to 2-amino-3-cyano-1*H*-indene in the presence of sodium ethoxide, and the latter was converted into 3-cyano-2-ethoxy-1*H*-indene by reaction with ethanol and sulfuric acid (17). Condensation of this cyano enol ether with guanidine (18) afforded IV in high yield. By a similar approach, a series of substituted 2-amino-3-cyano-1*H*-indenes was prepared and converted, *via* the corresponding 2-alkoxy-3-cyano-1*H*-indenes, into 2,4-diamino-9*H*-indeno[2,1-*d*]pyrimidines (V-X) (see Table I).

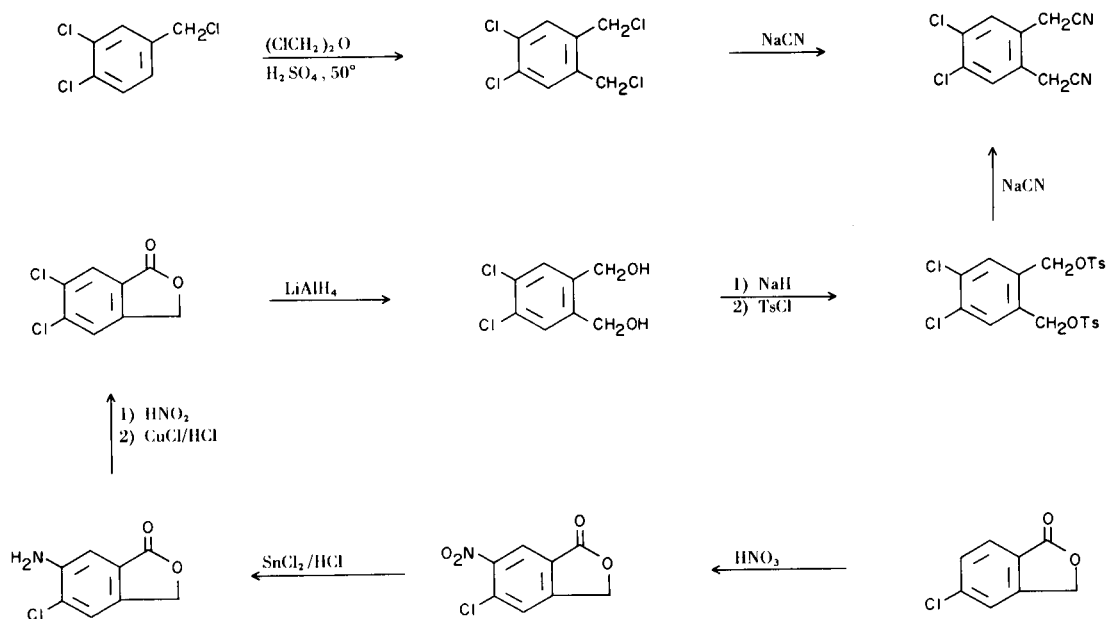
Substituted 1,2-bis(cyanomethyl)benzenes were prepared from the corresponding 1,2-bis(halomethyl)benzene derivatives. In some instances, 1,2-bis(chloromethyl) compounds were used; in others, it was more advantageous to use 1,2-bis(bromomethyl) compounds. Chloromethyl compounds were obtained *via* direct mono- or bischloromethylation of appropriate starting materials. The standard paraformaldehyde-hydrochloric acid reagent (19) was employed for the monochloromethylation of  $\alpha$ -chloro-*m*-xylene (20), and also for the bischloromethylation of *o*-xylene (21) and veratrole (22). Although the relatively unreactive *o*-dichlorobenzene could not be bischloromethylated with this reagent, success was achieved when the reaction was carried out with bis(chloromethyl) ether in concentrated sulfuric acid at 50° (23). Monochloromethylation of  $\alpha$ -chloro-*m*-xylene gave a mixture of 3,4- and 2,5-bis(chloromethyl) toluene (20). However, careful fractional distillation afforded the desired 3,4-bis(chloro-

methyl) isomer in a reasonable state of purity, as indicated by NMR and glpc. Bischloromethylation of *o*-disubstituted benzenes was shown by NMR to give symmetrical 4,5-disubstituted 1,2-bis(chloromethyl)benzenes predominantly. 1,2-Bis(bromomethyl) compounds used in this work included  $\alpha,\alpha'$ -dibromo-3-chloro-*o*-xylene and  $\alpha,\alpha'$ -dibromo-4-chloro-*o*-xylene. The synthesis of these strongly lachrymatory dibromides, as well as the preparation and cyclization of the corresponding dinitriles, has been reported elsewhere (24).

1,2-Bis(halomethyl) compounds were converted into dinitriles by reaction with sodium cyanide in dry dimethylsulfoxide or aqueous ethanol. In the case of 1,2-bis(halomethyl) compounds containing one or more aromatic chloro substituents, the latter solvent led to a cleaner reaction and a higher yield of product. Benzyl halides are oxidized by dimethylsulfoxide in the presence of a weak base, and the ease of oxidation is enhanced by aromatic chloro substituents (25). Symmetrical 4,5-disubstituted dinitriles could be differentiated readily from any possible position isomers by their NMR spectra, which showed the two benzylic methylene groups as a 4*H* singlet at  $\delta$  3.6-3.7 and the aromatic protons as a 2*H* singlet in the  $\delta$  6.9-7.6 region, depending upon the type of aromatic substituent. In one case, namely 4,5-dichloro-1,2-bis(cyanomethyl)benzene, the alternative synthesis shown in Scheme II was also carried out.

Cyclization of the substituted 1,2-bis(cyanomethyl)benzenes with sodium ethoxide (17) gave the desired 2-amino-3-cyano-1*H*-indenes in high yields (Table II). Optimum results were obtained when the reaction was performed under nitrogen in the minimum volume of absolute ethanol required to dissolve the dinitrile at reflux temperature. Upon contact with air, the reaction mixtures

SCHEME II



very rapidly turned purple and even black, indicating dimerization of the product (17). Very small amounts of colored impurities were sometimes detectable by the even after repeated recrystallizations. Infrared spectra of the cyclized products showed two strong bands in the 1560-1650  $\text{cm}^{-1}$  region, a band near 2200  $\text{cm}^{-1}$  (conjugated nitrile stretching), and three sharp bands in the 3250-3500  $\text{cm}^{-1}$  region. These spectral features indicate the products to be in the amino, rather than imino, form in the solid state.

Attempted direct cyclization of 2-amino-3-cyano-1*H*-indene by fusion with cyanamide in the presence of pyridine hydrochloride (3) failed to give IV. A close homolog, 2-amino-1-cyano-3,4-dihydronaphthalene, has been reported not to react under these conditions (5). Similar lack of reactivity of weakly basic *o*-aminonitriles toward carbon disulfide has been reported (26). Treatment of 2-amino-3-cyano-1*H*-indene with cyanoguanidine in the presence of sodium ethoxide gave only unreacted starting material, as did attempted fusion of the aminonitrile with cyanoguanidine at 180-185°. Since the 2-amino-3-cyano-1*H*-indenes could not be cyclized directly to the desired compounds, it was necessary to proceed by way of the corresponding 2-alkoxy-3-cyano-1*H*-indenes.

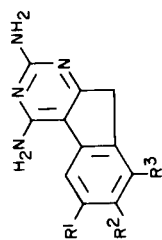
2-Amino-3-cyano-1*H*-indenes were converted into 2-alkoxy-3-cyano-1*H*-indenes (Table III) *via* two alternative routes. Treatment with ethanolic sulfuric acid, as described for the unsubstituted compound (17), effected direct replacement of the amino group by an ethoxy group. This one-step method was effective in the case of

the 5,6-dimethoxy and 5,6-dimethyl derivatives, but gave poor results with the 5-chloro compound. In the second approach, amino nitriles were converted into the corresponding cyano ketones (Table IV) by acid hydrolysis, and the latter were treated with ethereal diazomethane in a separate step.

The ease of acid hydrolysis of the 2-amino-3-cyano-1*H*-indenes depended markedly upon the nature of the aromatic substituents in the amino nitrile, and also upon the acid used and the duration of reflux. 2-Amino-3-cyano-1*H*-indene itself was converted into 1-cyano-2-indanone in high yield upon treatment with 2.4 *N* hydrochloric acid under reflux for only twenty minutes. On the other hand, as indicated in Table IV, hydrolysis of the 5,6-dichloro derivative required twenty hours of refluxing in 5 *N* hydrochloric acid. Numerous attempts to hydrolyze the 5-chloro compound with hydrochloric acid under a variety of conditions failed to give the desired cyano ketone cleanly. In this case, and also in the case of the 7-chloro analog, success was achieved by using 6 *N* sulfuric acid.

The hydrolysis of 2-amino-3-cyano-1*H*-indenes is obviously a complex reaction, since the resultant cyano ketones can undergo further hydrolysis to keto amides and/or keto acids, and the latter can be decarboxylated to 2-indanones. Competition from these unwanted side reactions becomes likely as the conditions needed to effect hydrolysis of the amino group increase in severity. Thus, under the conditions required for the preparation of 5,6-dichloro-1-cyano-2-indanone, there was also obtained

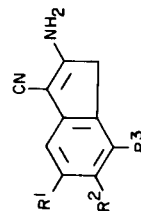
TABLE I



Compound	Substitution		R <sup>3</sup>	M.P., °C	Reaction time, hr.	Yield %	Formula	Calcd., %			Found, %				
	R <sup>1</sup>	R <sup>2</sup>						C	H	N	Cl	C	H	N	Cl
IV	H	H	H	224-225	3	92 (a)	C <sub>11</sub> H <sub>10</sub> N <sub>4</sub>	66.65	5.08	28.27		66.40	5.27	28.10	
V	CH <sub>3</sub>	CH <sub>3</sub>	H	274-276 dec.	3	58 (b)	C <sub>13</sub> H <sub>14</sub> N <sub>4</sub>	69.00	6.24	24.76		68.86	6.40	24.90	
VI	CH <sub>3</sub> O	CH <sub>3</sub> O	H	268-270 dec.	4	70 (c)	C <sub>13</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>	60.45	5.46	21.69		60.19	5.70	21.56	
VII	Cl	Cl	H	>280 dec.	4.5	45	C <sub>11</sub> H <sub>8</sub> Cl <sub>2</sub> N <sub>4</sub>	49.46	3.02	20.98	26.55	49.77	3.12	20.82	26.64
VIII	Cl	H	H	251-252 dec.	4	53	C <sub>11</sub> H <sub>9</sub> ClN <sub>4</sub>	56.78	3.90	24.08	15.24	57.09	3.98	23.86	15.42
LX	H	H	Cl	~295 dec.	5	62	C <sub>11</sub> H <sub>9</sub> ClN <sub>4</sub>	56.78	3.90	24.08	15.24	56.87	4.02	24.13	15.09
X	CH <sub>3</sub> (H)	H (CH <sub>3</sub> )	H	203-205 dec.	3	20	C <sub>12</sub> H <sub>12</sub> N <sub>4</sub>	67.90	5.70	26.40		67.59	5.83	26.36	

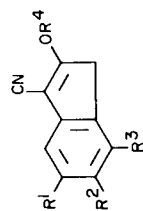
(a) Prepared from 3-cyano-2-ethoxy-1*H*-indene (18). (b) Prepared from 3-cyano-2-ethoxy-5,6-dimethyl-1*H*-indene. (c) Yield from the corresponding methyl enol ether. The ethyl enol ether had to be condensed with guanidine in the presence of sodium *n*-butoxide in butanol for eighteen hours to give a 71% yield of product; with sodium ethoxide in ethanol, 65% of the starting material was recovered.

TABLE II



R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	M.P., °C	Reaction time, min.	Yield %	Formula	Calcd., %			Found, %				
							C	H	N	Cl	C	H	N	Cl
CH <sub>3</sub>	CH <sub>3</sub>	H	243-244 dec.	50	86	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub>	78.23	6.57	15.21		78.40	6.57	15.06	
CH <sub>3</sub> O	CH <sub>3</sub> O	H	205-207 dec.	25	82	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	66.65	5.59	12.96		66.48	5.73	13.14	
Cl	Cl	H	278 dec.	3	86	C <sub>10</sub> H <sub>6</sub> Cl <sub>2</sub> N <sub>2</sub>	53.36	2.69	12.45	31.50	53.61	2.91	12.60	31.40
Cl	H	H	250-253 dec.	7	53 (24)	C <sub>10</sub> H <sub>7</sub> N <sub>2</sub> Cl	63.00	3.70	14.70	18.60	63.12	3.57	14.71	18.82
H	H	Cl	213-216 dec.	40	50 (24)	C <sub>10</sub> H <sub>7</sub> N <sub>2</sub> Cl	63.00	3.70	14.70	18.60	63.30	3.72	14.64	18.75
CH <sub>3</sub> (H)	H (CH <sub>3</sub> )	H	166-168 dec.	90	50	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub>	77.66	5.92	16.47		77.37	6.16	16.24	

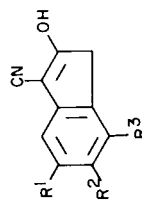
TABLE III



R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	M.P., °C	Yield %	Formula	Calcd., %	Found, %
							C H N Cl	C H N Cl
CH <sub>3</sub>	CH <sub>3</sub>	H	C <sub>2</sub> H <sub>5</sub>	106-108	50	C <sub>14</sub> H <sub>15</sub> NO	78.84 7.09 6.57	78.73 7.00 6.60
CH <sub>3</sub> O	CH <sub>3</sub> O	H	C <sub>2</sub> H <sub>5</sub>	130-132	44	C <sub>14</sub> H <sub>15</sub> NO <sub>3</sub>	68.55 6.16 5.71	68.52 6.20 5.60
CH <sub>3</sub> O	CH <sub>3</sub> O	H	CH <sub>3</sub>	182-184	82 (a)	C <sub>13</sub> H <sub>13</sub> NO <sub>3</sub>	67.52 5.66 6.06	67.62 5.74 6.12
Cl	Cl	H	CH <sub>3</sub>	165-168	51	C <sub>11</sub> H <sub>7</sub> Cl <sub>2</sub> NO	55.05 2.94 5.84 29.54	54.95 2.88 5.77 29.49
Cl	H	H	CH <sub>3</sub>	120-122	62 (d)	C <sub>11</sub> H <sub>8</sub> ClNO	64.24 3.92 6.81 17.24	64.39 4.05 6.54 17.48
H	H	Cl	CH <sub>3</sub>	140-142 dec.	63 (d)	C <sub>11</sub> H <sub>8</sub> ClNO	64.24 3.92 6.81 17.24	63.91 3.83 6.90 17.33
CH <sub>3</sub> (H)	H(CH <sub>3</sub> )	H	CH <sub>3</sub>	118-120 (b)	(c)	C <sub>12</sub> H <sub>11</sub> NO	77.81 5.99 7.56	77.67 6.20 7.49

(a) This product was insoluble in ether and was removed by filtration directly from the reaction mixture. (b) Softened > 114°. (c) The crude product was a brown oil which was obtained in quantitative yield. Short path distillation gave a few drops of orange oil, b.p. 139-145°/0.05 mm., which partially crystallized on standing. The crystalline material was suspended in carbon tetrachloride and then recrystallized from 95% ethanol. (d) Reference (24).

TABLE IV



R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	M.P., °C	Acid	Reaction time, hr.	Yield %	Formula	Calcd., %	Found, %
								C H N Cl	C H N Cl
CH <sub>3</sub>	CH <sub>3</sub>	H	178-180 dec.	conc. HCl	24	95 (a)	C <sub>12</sub> H <sub>11</sub> NO	77.82 5.99 7.56	77.57 5.86 7.72
CH <sub>3</sub> O	CH <sub>3</sub> O	H	179.5-180.5 dec	4N HCl	1	75	C <sub>12</sub> H <sub>11</sub> NO	66.35 5.10 6.45	66.27 5.18 6.53
Cl	Cl	H	208-210 dec.	5N HCl	20	82 (b)	C <sub>10</sub> H <sub>5</sub> Cl <sub>2</sub> NO	53.13 2.23 6.20 31.37	53.09 2.25 6.08 31.51
Cl	H	H	193-195 dec.	6N H <sub>2</sub> SO <sub>4</sub>	3	94 (c)	C <sub>10</sub> H <sub>6</sub> ClNO	62.68 3.16 7.31 18.50	62.77 3.32 7.16 18.57
H	H	Cl	206-209 dec.	6N H <sub>2</sub> SO <sub>4</sub>	3	94 (c)	C <sub>10</sub> H <sub>6</sub> ClNO	62.68 3.16 7.31 18.50	62.51 3.18 7.54 18.34
CH <sub>3</sub> (H)	H(CH <sub>3</sub> )	H	156-158 dec.	4N HCl	1	96	C <sub>11</sub> H <sub>9</sub> NO	77.19 5.30 8.18	77.22 5.26 8.18

(a) Obtained from material which had been refluxed in dilute hydrochloric acid for forty minutes and had m.p. ~220-230° dec. and was then kept in concentrated hydrochloric acid at room temperature. (b) 5,6-Dichloro-2-indanone was also obtained in 7.5% yield, m.p. 127-130°. *Anal.* Calcd. for C<sub>9</sub>H<sub>6</sub>Cl<sub>2</sub>O: C, 53.76; H, 3.00; Cl, 35.27. Found: C, 53.62; H, 3.09; Cl, 35.16. (c) Reference (24).

TABLE V  
Ultraviolet Spectra of 9*H*-Indeno[2,1-*d*]pyrimidines

Compound	95% EtOH	pH 1	pH 10
	$\lambda$ max, $m\mu$ (log $\epsilon$ )	$\lambda$ max, $m\mu$ (log $\epsilon$ )	$\lambda$ max, $m\mu$ (log $\epsilon$ )
IV	274 (4.34)	269 (4.34)	274 (4.34)
V	291 (4.31)	286 sh (4.13)	291 (4.31)
V	277 (4.30)	274 (4.28)	277 (4.30)
	297 (4.24)	290 sh (4.10) 295 sh (4.09)	297 (4.23)
VI	279 (4.30)	278 (4.24)	278 (4.44)
	306 (4.31)	302 (4.23)	292 sh (4.28) 304 sh (4.27)
VII	282 (4.47)	276 (4.50)	
	303 (4.40)	297 sh (4.24)	
VIII	238 sh (4.10)	218 (4.58)	
	277 (4.44)	272 (4.44)	277 (4.45)
	297 (4.31)	298 sh (4.04)	
IX	277 (4.40)	267 (4.40)	277 (4.41)
	295 sh (4.29)		293 sh (4.27)
X	275 (4.36)	272 (4.34)	
	298 (4.29)	285 sh (4.13)	

a small yield of 5,6-dichloro-2-indanone, which was identified by the characteristic carbonyl band of 2-indanones at  $1750\text{ cm}^{-1}$ , and by NMR and microanalysis. The intermediate 5,6-dichloro-2-indanone-1-carboxylic acid was obtained by pouring a solution of the amino nitrile in concentrated sulfuric acid into water. The infrared spectrum of the keto acid showed no nitrile band, but contained a series of strong bands in the  $1550\text{--}1640\text{ cm}^{-1}$  region, a broad band at  $2650\text{ cm}^{-1}$  (associated hydroxyl), and two sharp bands at  $3450$  and  $3550\text{ cm}^{-1}$  (free hydroxyl). As expected, this compound was quite unstable and could not be purified satisfactorily for analysis.

Although the 1-cyano-2-indanones prepared in this work are named as ketone derivatives, they are, in fact, enolic in the solid state, as evidenced by strong infrared bands near  $1620\text{ cm}^{-1}$  and  $3150\text{ cm}^{-1}$  in potassium chloride disks, and by the complete absence of carbonyl absorption. These observations are in accord with previously reported findings (17,27). Infrared spectra of the cyano enol ethers showed a characteristic conjugated nitrile band in the  $2210\text{ cm}^{-1}$  region, and a strong peak at about  $1590\text{ cm}^{-1}$ . NMR spectra of the enol ethers showed aromatic proton signals in the  $\delta$  7.1-7.7 region, and benzylic methylene protons in the  $\delta$  3.2-3.6 region. Enol ether methyl protons gave rise to a sharp singlet at  $\delta$  4.25. Enol ether ethyl protons showed a methylene quartet at  $\delta$  4.55 and a methyl triplet at  $\delta$  1.48. Compounds containing aromatic methyl or methoxy groups showed

additional signals at  $\delta$  2.28 and near  $\delta$  3.9, respectively. The signal ascribed to benzylic methylene protons tended to exhibit some fine structure, possibly because of long-range coupling to the C-7 aromatic proton. The NMR data for the methyl enol ethers showed that reaction of the cyano ketones with diazomethane led to *O*-alkylation, and not *C*-alkylation.

The synthesis of 2-alkoxy-3-cyano-1*H*-indenenes containing a single aromatic substituent merits special comment. The cyclization of symmetrical 4,5-disubstituted 1,2-bis-(cyanomethyl)benzenes was unambiguous, the cyanomethyl groups being equivalent. On the other hand, the cyclization of 3- or 4-monosubstituted dinitriles posed a directional problem, since two different anionic species could be generated in the presence of base. In the case of 3-chloro- and 4-chloro-1,2-bis(cyanomethyl)benzene, it was demonstrated that ring closure occurs unidirectionally, *via* anion formation on the cyanomethyl group *meta* to the chloro substituent (24). The identity of the cyclized products was established by hydrolysis, reaction with diazomethane, and oxidation of the resultant cyano enol ethers to monochlorohomophthalic acids, which were compared with authentic specimens.

The indenenes prepared from 4-methyl-1,2-bis(cyanomethyl)benzene by the usual sequence appeared to be single compounds, as evidenced by their sharp melting points, their behavior on tlc and glpc, and their infrared and NMR spectra. However, oxidation of the cyano enol

ether with chromic acid (24) yielded a mixture of 4- and 5-methylhomophthalic acids. The melting point of the oxidation product was 180-190°, whereas the melting points reported for 4- and 5-methylhomophthalic acid were 201° and 202°, respectively (28). A 1:1 mixture of the two pure acids (29) melted at 180-190°. Furthermore, although the infrared spectrum of the oxidation product could not be superimposed exactly upon that of either pure isomer, it was essentially identical with that of the 1:1 mixture. On this basis, it was concluded that the cyano enol ether derived from 4-methyl-1,2-bis(cyanomethyl)benzene was actually a mixture of 3-cyano-2-methoxy-5-methyl-1H-indene and 3-cyano-2-methoxy-6-methyl-1H-indene (see Table III). Since it could not be fractionated, this mixture of cyano enol ethers was converted directly into a mixture of isomeric monomethyl 2,4-diamino-9H-indeno[2,1-d]pyrimidines (see Table I). The fact that 4-methyl-1,2-bis(cyanomethyl)benzene did not cyclize unidirectionally indicates that the two cyanomethyl groups in this compound form anions with approximately equal ease, in contrast to the previously studied 3- and 4-chloro compounds (24). The lack of selectivity in the cyclization is consistent with the low Hammett  $\sigma$  values given for *m*- and *p*-methyl substituents (30).

The condensation of 2-alkoxy-3-cyano-1H-indenes with guanidine was performed according to the procedure of Russell and Hitchings (18). Yields were generally satisfactory (see Table I), and in some cases excellent. Despite the fact that reactions were carried out under a nitrogen atmosphere, considerable darkening was observed, probably as a result of base-catalyzed dimerization of the indenes (17). In addition, the products themselves showed evidence of light sensitivity, even after careful purification. The 2,4-diamino-9H-indeno[2,1-d]pyrimidines were characterized in the infrared by a series of strong bands in the region of 1570-1660  $\text{cm}^{-1}$ , and usually by three sharp bands near 3200, 3350, and 3450  $\text{cm}^{-1}$ . Their ultraviolet spectra (Table V) exhibited two maxima, one near 275  $\mu$  and the other near 300  $\mu$ . Both peaks underwent a small hypsochromic displacement at pH 1. In general, the spectral characteristics of the 2,4-diamino-9H-indeno[2,1-d]pyrimidines resembled those reported by Russell (31) for pyrimethamine and related compounds, but the maxima appeared at somewhat longer wavelengths.

The 2,4-diamino-9H-indeno[2,1-d]pyrimidines prepared in this work, together with other tricyclic pyrimethamine analogs of the type shown in structure 1, are being studied for antifolate and antitumor activity in these laboratories, and for antimalarial activity through the auspices of the Walter Reed Army Institute of Research. The results of these studies will be reported at a later date.

## EXPERIMENTAL

Ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Infrared spectra were taken in potassium chloride disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. NMR spectra were determined in deuteriochloroform solution on a Varian A-60 instrument, with tetramethylsilane as the internal reference. Glpc analyses were performed on an F & M Model 720 instrument, using helium as the carrier gas. Analytical samples were dried over Drierite at 70-100° (0.05 mm). Melting points were measured in Pyrex capillary tubes in a modified Wagner-Meyer apparatus (32) at a heating rate of 2°/minute, and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

### 1,2-Bis(cyanomethyl)-4,5-dimethylbenzene.

1,2-Bis(chloromethyl)-4,5-dimethylbenzene (21) (68.4 g., 0.34 mole) was dissolved in dimethylsulfoxide (600 ml., dried over Linde 4A molecular sieves). Sodium cyanide (36 g., 10% excess) was then added in small portions, the stirred mixture being cooled periodically in an ice bath in order to moderate the exothermic reaction. After the addition was complete, the yellow mixture was stirred under nitrogen overnight, diluted with cold water (700 ml.), and extracted with chloroform (2 x 300 ml.). The combined chloroform layers were washed with water, dried and evaporated. The residue was suspended in cold water (100 ml.) and filtered, 55 g. (89% yield) of yellow solid, m.p. 98-100°. Recrystallization from aqueous ethanol gave 48 g. (78% yield, 87% recovery) of 1,2-bis(cyanomethyl)-4,5-dimethylbenzene as a light yellow crystalline solid, m.p. 98-101°. Another recrystallization from aqueous ethanol afforded the analytical sample, m.p. 100-102°.

Anal. Calcd. for  $\text{C}_{12}\text{H}_{12}\text{N}_2$ : C, 78.23; H, 6.57; N, 15.21. Found: C, 78.04; H, 6.47; N, 15.13.

### 1,2-Bis(cyanomethyl)-4,5-dimethoxybenzene.

To a suspension of sodium cyanide (12 g., 10% excess) in dry dimethylsulfoxide (100 ml.) was added dropwise with stirring under nitrogen a solution of 1,2-bis(chloromethyl)-4,5-dimethoxybenzene (22) (26 g., 0.11 mole) in the same solvent (130 ml.). The initially exothermic reaction mixture was stirred overnight at room temperature, diluted with cold water (400 ml.), and extracted with chloroform (2 x 200 ml.). The combined chloroform layers were washed with water (100 ml.), dried, and evaporated to an orange oil which crystallized partially upon refrigeration. Filtration of the crystalline material gave 13 g. (53% yield) of dinitrile, m.p. 109-112°. Recrystallization from aqueous methanol gave 9.9 g. (75% recovery) of nearly colorless, shiny crystals, m.p. 118-120° (lit. (33) m.p. 120-121°). The remaining oil obtained above solidified on contact with ether, giving 6.2 g. of yellow solid, m.p. 112-120° after recrystallization from aqueous methanol. The total yield of once-crystallized material was 19.3 g. (81%).

### 1,2-Dichloro-4,5-bis(cyanomethyl)benzene.

#### Method A.

A mixture of 3,4-dichlorobenzyl chloride (55.8 g., 0.285 mole), bis(chloromethyl) ether (26.3 g., 0.229 mole), and concentrated sulfuric acid (40 ml.) was heated in a bath at 50-55° for two days, and poured into ice water (600 ml.). The organic material was extracted several times with dichloromethane (500 ml. total). The combined extracts were washed twice with water, separated from a small amount of insoluble brown material, dried, and

evaporated to a yellow oil which was fractionally distilled through a 25 cm. glass helices-packed column. The first fraction, b.p. 66-87° (0.06-0.07 mm.), contained only a trace of product. The main fraction, b.p. 88-107° (0.05-0.1 mm.), weighed 33.8 g. (49% yield) and consisted of 80% pure 1,2-dichloro-4,5-bis(chloromethyl)benzene, as shown by NMR and gas chromatographic analysis. This material was used directly in the next step.

1,2-Dichloro-4,5-bis(chloromethyl)benzene (28.8 g., 0.118 mole) was added to a solution of sodium cyanide (11.6 g., 0.237 mole) in 50% ethanol (70 ml.). After being refluxed for 30 minutes under nitrogen, the reaction mixture was diluted with dichloromethane, and poured into water. The organic layer was separated, and the aqueous layer extracted once more with dichloromethane. Evaporation of the dried organic layers gave a thick brown oil which underwent partial crystallization upon addition of ether. Filtration of the yellow solid and washing with ether gave 7.3 g. (33% estimated yield, based upon 80% pure starting material) of light yellow, somewhat sticky solid, m.p. about 80°. Recrystallization from 95% ethanol afforded 4.75 g. (65% recovery) of orange needles, m.p. 90-92°. The dinitrile obtained in this manner and the product synthesized *via* Method B (see below) were identical with respect to infrared and NMR spectra, and a mixed m.p. determination showed no depression. Method B. (See Scheme II).

5-Chlorophthalide (14 g., 0.08 mole), m.p. 156-158° (lit. (34) 154°), was added in small portions with stirring to an ice-cold mixture of fuming 90% nitric acid (300 ml.) and concentrated sulfuric acid (70 ml.). After being stirred for 30 minutes at 0°, the brown solution was allowed to come to room temperature and poured carefully onto crushed ice. Filtration of the precipitate, washing with ice water (4 x 500 ml.), and crystallization from ethanol gave 12 g. (70% yield) of 5-chloro-6-nitrophthalide as a yellow solid, m.p. 149-151° (lit. (35) 150-152°). This material (36 g., 0.17 mole) was added gradually to a stirred solution of stannous chloride (141 g., 0.75 mole) in 9*N* hydrochloric acid (1 liter). The mixture was stirred overnight at room temperature and neutralized with sodium carbonate. Filtration of the precipitate, washing with water, and drying gave 28 g. (91% yield) of crude 6-amino-5-chlorophthalide, m.p. 228-231°. Repeated crystallization of this material from dimethylformamide afforded the analytical sample, m.p. 277-278°. The lower-melting crude product was used directly in the next step.

*Anal.* Calcd. for C<sub>8</sub>H<sub>6</sub>ClNO<sub>2</sub>: C, 52.35; H, 3.29; N, 7.64. Found: C, 52.10; H, 3.27; N, 7.58.

Crude 6-amino-5-chlorophthalide (23 g., 0.12 mole) was dissolved in a mixture of 4 *N* hydrochloric acid (470 ml.) and acetonitrile (230 ml.), the latter being necessary to effect solution. The amine was diazotized at 0° by addition of 11.8 g. (0.17 mole) of sodium nitrite in water (95 ml.). The cold diazotized mixture was poured gradually with manual stirring into a large beaker containing a solution of 26 g. (0.26 mole) of cuprous chloride in 4 *N* hydrochloric acid (330 ml.). After foaming had subsided, the mixture was kept on the steam bath for 30 minutes. Filtration of the precipitate, washing with water, and drying gave 16 g. (64% yield) of crude 5,6-dichlorophthalide, m.p. 173-176°. Repeated crystallization from aqueous acetic acid afforded the analytical sample, m.p. 185-185.5°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>4</sub>Cl<sub>2</sub>O<sub>2</sub>: C, 47.36; H, 1.99; Cl, 34.85. Found: C, 47.45; H, 2.04; Cl, 34.73.

A 2-liter three-neck flask equipped with a mechanical stirrer, reflux condenser, and Soxhlet extractor (36) was charged with anhydrous ether (1250 ml.) and lithium aluminum hydride (19 g.,

0.54 mole). 5,6-Dichlorophthalide (20 g., 0.1 mole) was placed in the Soxhlet cup, and refluxing was started. After several days, during which nearly all the phthalide had been extracted, the reaction was quenched by careful addition of ice water. The entire mixture was then poured into ice-cold aqueous sodium sulfate (200 ml.). The ether layer was separated, and the aqueous phase was extracted with ether (2 x 300 ml.). Drying and evaporation of the combined ether layers gave 17 g. (82% yield) of crude 4,5-dichlorobenzene-1,2-dimethanol as a white solid, m.p. 117-122°. Two crystallizations from benzene gave 11 g. (65% recovery) of analytically pure diol, m.p. 142-142.5°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>Cl<sub>2</sub>O<sub>2</sub>: C, 46.40; H, 3.89; Cl, 34.25. Found: C, 46.40; H, 4.00; Cl, 34.24.

A solution of the above diol (11 g., 0.053 mole) in ether (110 ml.) was added dropwise to a stirred suspension of sodium hydride (5 g. of 50% dispersion in mineral oil, 0.11 mole) in ether (200 ml.) (37). After 36 hours, a heavy white precipitate was evident. To the mixture was then added rapidly a solution of *p*-toluenesulfonyl chloride (39 g., 0.2 mole) in ether (200 ml.), and stirring was continued at room temperature for 4 days. Unchanged sodium hydride was decomposed by careful dropwise addition of water (170 ml.). Drying and evaporation of the ether layer gave an oil. Upon being covered with ethanol and allowed to stand in the cold, the oil underwent partial solidification. Recrystallization of this solid from carbon tetrachloride-petroleum ether (b.p. 30-60°) afforded 11 g. (38% yield) of 4,5-dichlorobenzene-1,2-dimethanol ditosylate, m.p. 96-97°.

*Anal.* Calcd. for C<sub>22</sub>H<sub>20</sub>Cl<sub>2</sub>O<sub>6</sub>S<sub>2</sub>: C, 51.08; H, 3.91; Cl, 13.76; S, 12.42. Found: C, 50.97; H, 3.93; Cl, 14.00; S, 12.32.

A solution of the above ditosylate (5.2 g., 0.01 mole) in dry dimethylsulfoxide was added under a nitrogen atmosphere to a stirred suspension of sodium cyanide (1 g., 0.02 mole) in the same solvent. The total volume of solvent was 15 ml. A spontaneous rise in temperature to about 50° occurred during addition. After being stirred overnight, the dark mixture was poured into water (500 ml.), and the product was extracted several times with chloroform. The combined extracts were dried and evaporated at 0.05 mm. to remove the last traces of dimethylsulfoxide. The dark oily residue (3 g.) was taken up in ethanol and the solution treated several times with decolorizing carbon. Dilution with water gave 0.43 g. (10% yield) of 1,2-dichloro-4,5-bis(cyanomethyl)benzene as a yellow solid, m.p. 94-95°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>6</sub>Cl<sub>2</sub>N<sub>2</sub>: C, 53.36; H, 2.69; Cl, 31.46; N, 12.45. Found: C, 53.25; H, 2.70; Cl, 31.74; N, 12.30.

#### 3,4-Bis(cyanomethyl)toluene.

A mixture of  $\alpha$ -chloro-*m*-xylene (90 g., 0.64 mole), paraformaldehyde (55 g., 1.35 mole), and concentrated hydrochloric acid (450 ml.) was refluxed for 42 hours with vigorous mechanical stirring. The reaction mixture was cooled and extracted with ether. The ether extract was washed twice with water, once with dilute sodium bicarbonate, and twice more with water. Evaporation of the dried solution gave a light yellow oil which was fractionated by means of a 20 cm. Vigreux column. Fractions were analyzed by glpc on a 6 ft. x ¼ in. LAC-728 polyester column. The first fraction, b.p. 29-33° (0.1-0.2 mm.), consisted only of starting material (16 g., 18% recovery). The second fraction, b.p. 65-70° (0.05 mm.), consisted of a 2:1 mixture of 3,4-bis(chloromethyl)toluene and 2,5-bis(chloromethyl)toluene. This fraction weighed 62 g., of which 41 g. (41% yield, based on starting material consumed) was the desired 3,4-bis(chloromethyl)isomer. A higher-boiling fraction, as well as the residue in the distilling flask, solidified. This material consisted mainly of the 2,5-bis(chloro-



methyl)isomer. A second fractionation of the main fraction through a 25 cm. column packed with 3/16" glass helices gave a small forerun, b.p. 57° (0.05 mm.), followed by the main fraction, b.p. 65-70° (0.05 mm.), which weighed 48 g. Glpc analysis showed this material to contain 38 g. (38% yield, based on consumed starting material) of 3,4-bis(chloromethyl)toluene (20).

The impure 3,4-bis(chloromethyl)toluene (48 g., 0.25 mole) was dissolved in dry dimethylsulfoxide (120 ml.), and the solution was added gradually to a stirred suspension of sodium cyanide (27.5 g., 10% excess) in the same solvent (100 ml.). The reaction was exothermic. After being stirred at room temperature for 4 hours, the orange mixture was diluted with chloroform (200 ml.) and water (400 ml.), and the chloroform layer was removed. The aqueous phase was extracted again with chloroform (100 ml.), and the combined chloroform extracts were washed with water. Drying and evaporation gave a viscous brown oil which could not be distilled. Glpc analysis showed the disappearance of the starting dichloro compound, and the appearance of a major peak (75% of the total area) with a much longer retention time, which was ascribed to the desired dinitrile. The crude oil (41 g.) was used directly in the cyclization step.

Oxidation of 3-cyano-2-methoxy-5(and 6)-methyl-1H-indene.

The mixture of enol ethers (1 g., 0.0055 mole) was dissolved in glacial acetic acid (30 ml.) and treated with chromium trioxide (1.1 g., 0.011 mole, 2 equivalents) on the steam bath for 45 minutes. The dark mixture was poured into ice water (450 ml.), and a trace of dark brown insoluble residue was filtered off. The filtrate was extracted twice with ether (200 ml. total), and the yellow ether extract was washed twice with water, dried, and evaporated. The residue was then hydrolyzed with 10% sodium hydroxide (20 ml.) on the steam bath for 30 minutes. The brown solution was cooled, acidified, and extracted three times with ether, and the ether extract was washed with water. Evaporation gave 0.35 g. (33% yield) of light beige solid, m.p. about 180-190°. The infrared spectrum of this material was not exactly superimposable upon that of either pure 4-methyl or pure 5-methylhomophthalic acid (29), but was identical with that of a 1:1 mixture of the acids. This mixture likewise melted at about 180-190°. Recrystallization of the oxidation product from water gave light yellow needles, m.p. about 188-193°. On the basis of the infrared spectrum, this appeared to be a mixture somewhat enriched in 4-methylhomophthalic acid. A complete separation of the isomers by fractional crystallization was not possible. The mixed acids were converted into dimethyl esters by reaction with diazomethane, and separation was attempted by glpc on 10% SE-30 silicone gum, 10% Carbowax 20M, 10% LAC-728 diethylene glycol succinate, 10% Apiezon L, 8% EGSS-X ethylene glycol succinate, and 10% diisodecyl phthalate. In no case was it possible to effect separation of the isomeric dimethyl esters.

General Procedures.

2-Amino-3-cyano-1H-indenes (Table II).

Solutions of the appropriate 1,2-bis(cyanomethyl)benzene in the minimum volume of refluxing absolute ethanol were prepared, and sodium ethoxide in ethanol (0.2 g. of sodium per 10 ml. of absolute ethanol) was added under an atmosphere of nitrogen. The reaction mixtures generally darkened rapidly, and in most cases the products precipitated from solution after a short time. After being refluxed with stirring for periods ranging from 5 minutes to 1 hour, the mixtures were cooled in ice, and the products filtered and recrystallized from ethanol.

1-Cyano-2-indanones (Table IV).

Suspensions of the 2-amino-3-cyano-1H-indenes in aqueous hydrochloric or sulfuric acid were refluxed with stirring for periods ranging from 1 hour to 20 hours. The hydrolysis mixtures were cooled in ice, diluted with water, and filtered, and the products were recrystallized from aqueous ethanol.

3-Cyano-2-methoxy-1H-indenes (Table III).

Slurries of the 1-cyano-2-indanones in ether were treated with freshly prepared ethereal diazomethane (38) until gas evolution ceased. Brown solutions were obtained in most cases. Traces of insoluble material were removed by filtration, and the filtrates were evaporated. The products were recrystallized from ethanol.

3-Cyano-2-ethoxy-1H-indenes (Table III).

Suspensions of the 2-amino-3-cyano-1H-indenes (0.01 mole) in absolute ethanol (100 ml.) under nitrogen were treated with concentrated sulfuric acid (30 ml.) to give clear solutions at the reflux temperature. After 30 minutes of refluxing, the mixtures were kept at room temperature overnight, poured into ice water (600 ml.), and extracted with ether (200 ml.). The ether extracts were washed with water, dried, and evaporated, and the products were recrystallized from ethanol.

2,4-Diamino-9H-indeno[2,1-d]pyrimidines (Table I).

Guanidine solutions were prepared by treating pulverized guanidine hydrochloride (1.5 equivalents) with sodium ethoxide (1.2 equivalents) in absolute ethanol, and filtering off the sodium chloride. The guanidine solutions were then added rapidly to refluxing solutions of the 3-cyano-2-alkoxy-1H-indenes (1.0 equivalent) in absolute ethanol under nitrogen. The dark reaction mixtures were stirred under reflux for 3-5 hours, cooled, and filtered, and the products were recrystallized from ethanol. The ultraviolet absorption maxima of the products are listed in Table V.

Acknowledgment.

The authors are indebted to Miss Katherine K. N. Chen and Mrs. Rebecca G. Stephenson for their invaluable laboratory assistance, and to Mr. Roger Cavallo and Mr. Chester Rosansky for determining the quantitative ultraviolet spectra reported here.

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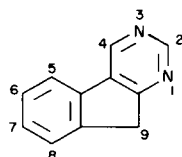
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Received May 26, 1969

Boston, Massachusetts 02115