Preparation of 4,6-Diaminopyrazolo[3,4-*d*]pyrimidines with Variations in Substitution at the 1- and 3-Positions (1)

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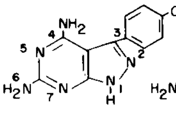
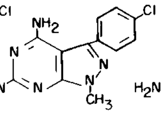
A number of new derivatives of 4,6-diaminopyrazolo[3,4-*d*]pyrimidines substituted in the 1- and/or 3-positions have been obtained from reactions of guanidine carbonate with 1- and/or 3-substituted-5-amino-4-cyanopyrazoles. Use of triethanolamine as a reaction medium permitted preparation of certain derivatives which could not be obtained from the previously described fusion procedure. Some derivatives of 4-aminopyrazolo[3,4-*d*]pyrimidine with substitution at the 1- and/or 3-positions were also obtained from reactions of formamide with the same 5-amino-4-cyanopyrazoles. The new compounds were screened for *in vivo* antimalarial activity, but were found inactive.

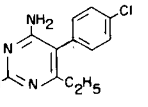
4,6-Diamino derivatives of pyrazolo[3,4-*d*]pyrimidine incorporate the 2,4-diaminopyrimidine structure and might appear to hold promise as potential folate antagonists (2). For this reason a group of 4,6-diamino derivatives of this system were prepared with variations in the substituent groups in positions 1 and 3. The 3-*p*-chlorophenyl derivatives Il and In, for example, can be seen to have a rather close structural relationship to pyrimethamine, and were therefore selected as primary synthetic goals. However, derivatives with other substituents and combinations of substituents in the 1- and 3- positions were also sought in order to assess adequately the promise of the ring system as a possible source of folate antagonists having antimalarial activity. 4,6-Diaminopyrazolo[3,4-*d*]pyrimidine derivatives with three substitution patterns and 4-aminopyrazolo[3,4-*d*]pyrimidine derivatives also with three substitution patterns were secured during the course of the investigation.



Il



In



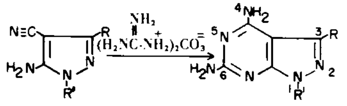
pyrimethamine

A few 4,6-diaminopyrazolo[3,4-*d*]pyrimidines had been synthesized previously. Cheng and Robins (3) had prepared the 1-methyl and 1-phenyl derivatives from the 1-methyl- and 1-phenyl-5-amino-4-cyanopyrazoles *via* corresponding 4,6-dihydroxy and 4,6-dichloropyrazolo[3,4-*d*]pyrimidine derivatives. Davoll and Kerridge (4) described a one-step synthesis of 4,6-diaminopyrazolo[3,4-*d*]pyrimidine itself from 5-amino-4-cyanopyrazole by fusion with guanidine carbonate (5). We have found that the method of Davoll and Kerridge can be extended to produce a variety of 1-and/or 3-substituted 4,6-diaminopyrazolo[3,4-*d*]pyrimidines. As an initial test of the method 1-phenyl-4,6-diaminopyrazolo[3,4-*d*]pyrimidine was prepared by fusion of 1-phenyl-5-amino-4-cyanopyrazole with guanidine carbonate. The properties of the product were in full agreement with those previously reported for 1-phenyl-4,6-diaminopyrazolo[3,4-*d*]pyrimidine by Cheng and Robins (3), and an nmr spectrum confirmed the assigned structure (δ 7.55 (s, 5, aromatic), 8.70 (s, 1, H at 3-position)). The yield of 60% was somewhat higher than the 50% overall yield reported for the four-step sequence (3) from 1-phenyl-5-amino-4-cyanopyrazole.

We modified the simple fusion procedure of Davoll and Kerridge in two ways. In most instances the fused mixtures of guanidine carbonate with the 1- and/or 3-substituted-5-amino-4-cyanopyrazoles were maintained under somewhat reduced pressure during the reaction period to reduce exposure of the mixtures to atmospheric oxygen and remove water formed in the reaction. A further modification, use of triethanolamine as the reaction medium, was needed in order to achieve reasonable yields of two of the compounds, the 1-(3-chloro-4-methylphenyl) and 1-(4-chloro-2-methylphenyl) derivatives Ii and Ij. In the case of Compound Ii the 4% yield obtained by the fusion procedure was raised to 70% by conducting the reaction in the presence of triethanolamine. Compound Ij could not be isolated at all in the case of attempts to use the original fusion procedure, but a 57% yield was obtained with added

Table I

Preparation of 4,6-Diaminopyrazolo[3,4-*d*]pyrimidines

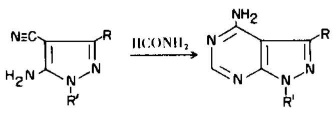


No.	R	R′	M.p. °C	Reaction temp/time (hours)	Yield %, Procedure (a)	Formula	Analysis					
							Calcd.			Found		
							C	H	N	C	H	N
Ia	H	*p*-ClC_6H_4	302-305	165-170/1½	76-F	$C_{11}H_9N_6Cl$	50.67	3.45	32.25	50.68	3.65	31.98
Ib	H	3,4-$Cl_2C_6H_3$	289-290	170-185/1½	62-F	$C_{11}H_8N_6Cl_2$	44.75	2.71	28.47	44.83	2.63	28.42
Ic	H	2,4-$Cl_2C_6H_3$	301-302	155-165/2½	57-F	$C_{11}H_8N_6Cl_2$	44.75	2.71	28.47	44.76	2.97	28.67
Id	H	2-CH_3-4ClC_6H_3	275-276	160-180/2	37-F	$C_{12}H_{11}N_6Cl$	52.46	4.00	30.60	52.45	4.12	30.74
Ie	H	4-CH_3-3ClC_6H_3	242-242.5	210-230/2	70-F	$C_{12}H_{11}N_6Cl$ (b)	52.46	4.00	30.60	52.50	3.85	30.49
If	H	$HOCH_2CH_2$	258-259	150-160/2½	52-F (c)	$C_7H_{10}N_6O$	43.29	5.19	43.28	43.22	4.89	43.57
Ig	CH_3	*p*-ClC_6H_4	250-251	170-180/2	32-F	$C_{12}H_{11}N_6Cl$	52.46	4.00	30.60	52.60	3.87	30.59
Ih	CH_3	3,4-$Cl_2C_6H_3$	289.5-290	220-230/3	42-F	$C_{12}H_{10}N_6Cl$	46.60	3.23	27.18	46.66	3.18	26.97
Ii	CH_3	4-CH_3-3ClC_6H_3	224-225	180/1 and then 200-220/2	70-T	$C_{13}H_{13}N_6Cl$ (d)	54.07	4.51	29.10	53.88	2.55	29.15
Ij	CH_3	2-CH_3-4ClC_6H_3	227-228	180-190/3	57-T	$C_{13}H_{13}N_6Cl$	54.07	4.51	29.10	53.97	4.52	28.97
Ik	CH_3	$HOCH_2CH_2$	267-269	180-195/3	64-F (c)	$C_8H_{12}N_6O$	46.15	5.77	40.38	46.44	5.54	40.61
Il	*p*-ClC_6H_4	H	332-335	220-235/2	39-F	$C_{11}H_9N_6Cl$	50.67	3.45	32.25	50.58	3.62	31.99
Im	C_6H_5	CH_3	199-200	160-180/2½	36-F (e)	$C_{12}H_{12}N_6$	59.98	5.03	34.98	59.83	5.21	35.15
In	*p*-ClC_6H_4	CH_3	248.5-249.5	170-175/3	28-F	$C_{12}H_{11}N_6Cl$ (f)	52.46	4.00	30.60	52.44	4.03	30.45
Io	*p*-$CH_3C_6H_4$	CH_3	272-273	180-185/2	54-F	$C_{13}H_{14}N_6$	61.39	5.55	33.05	61.15	5.35	33.30
Ip	*p*-$CH_3OC_6H_5$	CH_3	262-263	190-200/2½	39-F	$C_{13}H_{14}N_6O$	57.76	5.22	31.10	57.78	5.30	31.31
Iq	*p*-ClC_6H_4	$HOCH_2CH_2$	234-235	175-185/3	44-F	$C_{13}H_{13}N_6ClO$	51.23	4.27	27.59	51.31	4.02	27.80
Ir	*p*-$ClC_6H_4CH_2$	H	269-270	165-175/2½	45-F	$C_{12}H_{11}N_6Cl$ (g)	52.46	4.00	30.60	52.20	3.89	30.80
Is	*p*-$CH_3OC_6H_4CH_2$	H	250-251	170-180/3	45-F (e)	$C_{13}H_{14}N_6O$	57.76	5.22	31.10	57.70	5.22	30.82

(a) F = fusion procedure; T = triethanolamine procedure. (b) Ir: 2.90, 3.00, 3.18 (NH), 6.05, 6.15, 6.30, 6.70, 7.35, 8.64, 9.12, 9.54, 10.36, 11.50, 12.20, 12.66, 13.82 μ. Nmr (δ): 2.48 (s, 3, CH_3), 7.25-7.70 (m, 3, aromatic); 8.70 (s, 1, H at 3-position). (c) Recrystallized from water. (d) Ir: 2.85, 2.94, 2.99, 3.20 (NH), 6.02, 6.10, 6.18, 6.25, 6.58, 8.75, 9.14, 9.54, 10.14, 11.38, 12.30, 12.64 μ. Nmr (δ): 2.53 (s, 3, Ar-C*H*$_3$), 2.80 (s, 3, C*H*$_3$ at 3-position), 7.3-7.65 (m, 3, aromatic). (e) Recrystallized from ethanol. (f) Ir: 2.86, 2.94, 3.00, 3.12 (NH), 6.08, 6.16, 6.24, 6.30, 6.34, 6.40, 6.64, 9.16, 9.90, 10.16, 10.94, 11.80, 12.14, 12.56, 13.08, 13.92 μ. Nmr (δ): 4.15 (s, 3, CH_3), 7.68 (s, 4, aromatic). (g) Ir: 2.95, 3.00, 3.10 (NH), 6.15, 6.36, 9.16, 9.82, 11.68, 12.68, 13.20 μ. Nmr (TFA/deuteriochloroform): 4.48 (s, 2, CH_2), 7.13-7.53 (q, AB type, 4, J = 8 Hz).

Table II

Preparation of 4-Aminopyrazolo[3,4-*d*]pyrimidines

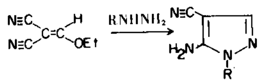


R	R′	M.p. °C	Yield %, (a)	Formula	Analysis Calcd. C	H	N	Found C	H	N
H	*m*-Cl-C_6H_4	242-243	59 (B)	$C_{11}H_8ClN_5$	53.77	3.26	28.51	53.92	3.07	28.35
p-$ClC_6H_4CH_2$	H	274-276	72 (A)	$C_{12}H_{10}ClN_5$	55.49	3.85	26.97	55.24	3.83	26.88
p-ClC_6H_4	CH_3	262-262.5	72 (B)	$C_{12}H_{10}ClN_5$	55.49	3.85	26.97	55.55	4.07	26.86
3,4-$Cl_2C_6H_4$	CH_3	259-260	54 (A)	$C_{12}H_9Cl_2N_5$	48.98	3.06	23.81	48.85	2.87	23.88
2,4-$Cl_2C_6H_4$	CH_3	229-230	63 (A)	$C_{12}H_9Cl_2N_5$	48.98	3.06	23.81	48.79	3.32	23.64

(a) A indicates crystallization from aqueous ethanol; B, from absolute ethanol. (b) Ir: 2.90, 3.00, 3.15 (NH), 6.08, 6.30, 7.62, 7.92, 9.14, 9.88, 10.00, 10.80, 11.12, 12.40, 12.80, 13.80 μ. Nmr (δ): 4.52 (s, 2, C*H*₂), 7.13-7.54 (q, AB type, 4, J = 9 Hz, aromatic), 8.65 (H at 3-position).

Table III

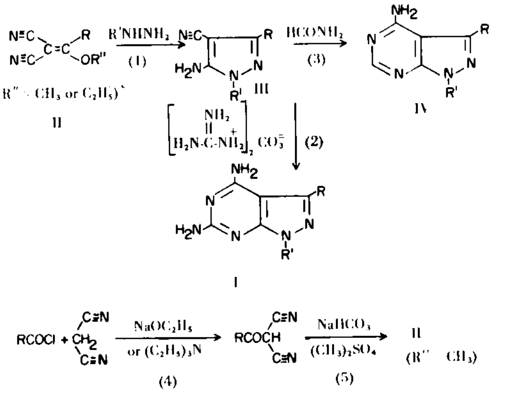
Preparation of 1-Substituted-5-amino-4-cyanopyrazoles



R	M.p. °C	Crystallization Solvent	Yield, %	Formula	Analysis Calcd. C	H	N	Found C	H	N
p-ClC_6H_4-	173-174 (a)	EtOH	80	$C_{10}H_7ClN_4$	54.93	3.23	25.63	54.69	3.46	25.68
m-ClC_6H_4-	188-189	EtOH	73	$C_{10}H_7ClN_4$ (b)	54.93	3.23	65.63	54.86	3;31	25.59
3,4-$Cl_2C_6H_3$-	187.5-188.5	EtOH	60	$C_{10}H_6Cl_2N_4$	47.43	2.37	22.13	47.61	2.34	22.01
2,4-$Cl_2C_6H_3$-	141-142	EtOH-H_2O	70	$C_{10}H_6Cl_2N_4$	47.43	2.37	22.13	47.27	2.52	22.04
2-CH_3-4-ClC_6H_3-	130-131	M-P (c)	64	$C_{11}H_9ClN_4$	56.77	3.87	24.08	56.68	3.67	24.01
4-CH_3-3-ClC_6H_3-	194-195	EtOH	79	$C_{11}H_9ClN_4$	56.77	3.87	24.08	56.83	3.94	23.88
$HOCH_2CH_2$-	160-161 (d)	EtOH	61	$C_6H_8N_4O$						

(a) Lit. m.p. 167-167.5° (Ref. 2). (b) Ir: 2.84, 2.98, 3.08 (NH), 4.42 (C≡N), 6.04, 6.22, 6.36, 6.48, 9.05, 9.25, 9.54, 10.44, 11.26, 11.50, 12.54, 12.66, 13.35, 14.52 μ. Nmr (δ): 7.3-7.8 (m, 4, aromatic); 8.06 (H at 3-position). (c) A mixture of methylene chloride and low-boiling (30-60°) petroleum ether. (d) Lit. m.p. 158-160° (Ref. 2).

Chart I



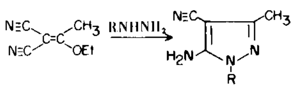
triethanolamine. Compound Ij also failed to form when the amino cyano pyrazole was heated with guanidine in refluxing ethanol for twenty hours. Table I summarizes results obtained in the preparation of the various types of 4,6-diaminopyrazolo[3,4-*d*]pyrimidine derivatives. Chart I outlines the reactions which were utilized in the complete synthetic sequence.

The new 4-amino derivatives of pyrazolo[3,4-*d*]pyrimidine (IV) which were synthesized were obtained in satisfactory yields by refluxing 5-amino-4-cyanopyrazole derivatives with formamide (reaction (3) in Chart I) (6). Results are recorded in Table II.

The 5-amino-4-cyanopyrazole derivatives used as inter-

Table IV

Preparation of 1-Substituted-5-amino-4-cyano-3-methylpyrazoles



R	M.p. °C	Crystallization Solvent	Yield, %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
p-Cl-C_6H_4-	176-177	EtOH	68	$C_{11}H_9ClN_4$ (a)	56.77	3.87	24.08	56.81	3.71	23.86
2,4-Cl_2-C_6H_3-	192-193	M-P (b)	75	$C_{11}H_8Cl_2N_4$	49.44	3.00	20.97	49.25	3.25	20.72
3,4-Cl_2-C_6H_3-	236-237	EtOH	88	$C_{11}H_8Cl_2N_4$	49.44	3.00	20.97	46.92	2.99	20.97
4-CH_3-3-Cl-C_6H_3-	197-198	EtOH	72	$C_{12}H_{11}ClN_4$	58.42	4.46	22.72	58.35	4.42	22.92
2-CH_3-4-Cl-C_6H_3-	160-161	EtOH	81	$C_{12}H_{11}ClN_4$	58.42	4.46	22.72	58.64	4.22	22.71
HO-CH_2CH_2-	176-176.5	EtOH	60	$C_7H_{10}N_4O$	50.69	6.02	33.74	50.39	6.01	33.76

(a) Ir: 2.88, 3.01 (NH), 4.50 (C≡N), 6.10, 6.26, 6.41, 6.52, 7.59, 8.26, 8.52, 9.15, 9.36, 9.86, 11.82, 11.92, 13.45 μ. Nmr (δ): 2.66 (s, 3, C*H*$_3$), 7.45-7.84 (q-AB type, 4, J = 9 Hz, aromatic). (b) A mixture of methylene chloride and low-boiling (30-60°) petroleum ether.

mediates were obtained from reactions of appropriately substituted ethoxy- or methoxymethylene derivatives of malononitrile with hydrazine or substituted hydrazines essentially by the method developed by Robins (6) and Cheng and Robins (7a). The arylmethoxymethylenemalononitriles used were prepared from malononitrile by the reactions indicated in the second sequence in reaction Chart I (8). For acylation of malononitrile by aroyl chlorides we found sodium ethoxide in a benzene-ethanol mixture to be the most efficient base. (*Cf.* Libis and Fleury, reference 8a). Improved results were also achieved by modification of previous procedures for *O*-methylation of the enolic acylmalononitriles. Results obtained in the preparation of the 5-amino-4-cyanopyrazoles are recorded in Tables III, IV, and V.

All of the compounds listed in Tables I and II were found inactive when screened for suppression of malarial infection by *Plasmodium berghei* in mice (9a). Compounds Il and Im were also assayed against a sporozoite-induced *Plasmodium gallinaceum* infection in chicks (9b), but again failed to display activity.

EXPERIMENTAL (10)

1-Substituted-5-amino-4-cyanopyrazoles.

An arylhydrazine hydrochloride was added to an equimolar quantity of 0.5 molar enthanolic sodium ethoxide. An equimolar amount of ethoxymethylenemalononitrile was then added in small portions and the mixture was refluxed for 30 minutes on a steam-bath. The mixture was then cooled and the product was collected by filtration. The crude sample was crystallized from ethanol or a methylene chloride-petroleum ether mixture. As essentially similar procedure to that just described for 1-aryl derivatives gave the 1-(2-hydroxyethyl) derivative from 2-hydroxyethylhydrazine. Yields were in the range 60-80%. Results are compiled in Table III (11).

1-Substituted-5-amino-3-methyl-4-cyanopyrazoles.

An arylhydrazine hydrochloride was added to an equimolar quantity of 0.4 molar ethanolic sodium ethoxide. Methylethoxymethylenemalononitrile (7a) in equimolar amount was then added slowly and the solution was refluxed for 30 to 60 minutes. It was then cooled, the precipitate was collected by filtration, and sodium chloride was removed from it by washing with water. The products were purified by recrystallization from ethanol. (A similar procedure was used with 2-hydroxyethylhydrazine.) The yeilds were in the range 60-90%. Results are compiled in Table IV (12).

3-(Aryl or Benzyl)-5-amino-4-cyanopyrazoles. Aroylmalononitriles. Procedure A. (*Cf.* B. Libis and J. P. Fleury, reference 8a).

An aromatic acid chloride (0.33 mole) and malononitrile (0.33 mole) were dissolved in 300 ml. of anhydrous benzene. Triethylamine (0.66 mole) dissolved in 4-6 parts of benzene (*ca.* 400-500 ml.) was then added in small portions with vigorous stirring. Stirring was continued for 2 hours. The mixture was filtered to remove the triethylamine hydrochloride, and the lower liquid layer was separated from the benzene (upper) layer and concentrated as completely as possible over a steam bath on a rotatory evaporator. Sulphuric acid (2*N*, 1 l.) was then added to the oil and the mixture was extracted with 150 ml. of ether. The ether extract was dried (sodium sulfate), and evaporated to yield a yellow solid. Recrystallization from suitable solvents then gave pure products. The previously described products benzoylmalononitrile (8a), *p*-chlorobenzoylmalononitrile (8a, 8b), *p*-toluoylmalononitrile (8a) and *p*-methoxybenzoylmalononitrile (8a) were prepared by this method, as well as the one new compound described below.

3,4-Methylenedioxybenzoylmalononitrile.

The yield from 0.24 mole of the acid chloride was 24 g. (47%), m.p. 173-174° (crystallized from methylene chloride-petroleum ether (b.p. 30-60°); ir: 2.90 (OH), 4.47, 4.51 (C≡N), 6.16, 6.22, 6.38, 6.64, 7.76, 7.84, 8.26, 9.12, 9.56, 10.44, 10.76, 11.40, 12.24, 13.78, 14.24.

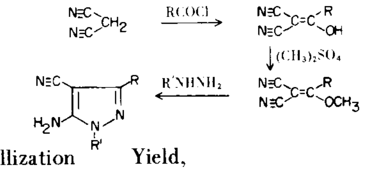
Anal. Calcd. for $C_{11}H_6O_3N_2$: C, 61.68; H, 2.82; N, 13.08. Found: C, 61.47; H, 2.84; N, 12.80.

Procedure B.

A procedure which was somethat more convenient than proce-

Table V

Preparation of 1-Substituted-5-amino-3-aryl or Benzyl-4-cyanopyrazoles



R	R'	M.p. °C	Crystallization Solvent	Yield, %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	CH_3	133.5-134	H_2O	76	$C_{11}H_{10}N_4$	66.65	5.09	28.27	66.74	5.27	28.50
p-ClC_6H_4-	CH_3	163.5-164.5	M-P (a)	69	$C_{11}H_9ClN_4$ (b)	56.77	3.87	24.08	56.64	3.61	23.86
p-Cl-C_6H_4-	H	214-215 (c)	EtOH	100	$C_{10}H_7ClN_4$						
p-$CH_3C_6H_4$-	CH_3	161-162	EtOH-H_2O	78	$C_{12}H_{12}N_4$	67.90	5.70	26.40	67.97	5.50	26.17
p-CH_3O-C_6H_4-	CH_3	182-183	M-P (a)	66	$C_{12}H_{12}N_4O$	63.14	5.30	24.55	62.95	5.15	24.33
3,4-OCH_2O-C_6H_3-	CH_3	252-254	EtOH	36 (d)	$C_{12}H_{10}N_4O_2$	59.50	4.16	23.13	59.72	4.38	23.00
p-Cl-C_6H_4-	$HOCH_2CH_2$	171-172	EtOH	57.2	$C_{12}H_{11}ClN_4O$	54.86	4.19	21.33	55.04	4.09	21.26
p-CH_3O-$C_6H_4CH_2$-	H	147-148	H_2O	23 (e)	$C_{12}H_{12}N_4O$	63.14	5.30	24.55	63.31	5.17	24.59
p-Cl-$C_6H_4CH_2$-	H	166-167	H_2O	23 (e)	$C_{11}H_9N_4Cl$	56.77	3.87	24.09	56.60	4.03	23.93

(a) A mixture of methylene chloride and low boiling (30-60°) petroleum ether. (b) Ir: 2.82, 2.98, 3.06 (NH), 4.48 (C≡N), 6.06, 6.35, 6.56, 6.60, 7.72, 9.14, 9.86, 11.86, 12.20, 13.52, 13.66, 13.84 μ. Nmr (δ) (deuteriochloroform): 3.69 (s, 3, CH_3); 4.0-4.5 (br, 2, NH_2) 7.28-7.89 (q-AB type, 4, J = 9 Hz, aromatic). (c) Lit. (Ref. 8d) m.p. 212°. (d) Yield based on aroylmalononitrile. (e) Yield based on original arylacetic acid.

dure A was applied successfully to the preparation of several of the same derivatives. The preparation of the *p*-toluoyl derivative described below is illustrative of the method.

p-Toluoylmalononitrile.

Sodium (2.3 g., 0.1 mole) was dissolved in 60 ml. of ethanol and malononitrile (3.3 g., 0.05 mole) dissolved in a small volume (5-10 ml.) of ethanol was added. *p*-Toluoyl chloride (7.7 g., 0.05 mole) dissolved in 50 ml. of benzene was added in small portions. After stirring for 1 hour, the solvent was evaporated. The pinkish residual sodium salt was treated with 250 ml. of 2*N* sulfuric acid and the solid that separated was filtered, m.p. *ca.* 185°. Two recrystallizations from nitromethane gave a colorless crystalline solid, m.p. 192-194°, yield, 6.4 g. (70%).

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.82; H, 4.,6; N, 14.98.

Libis and Fleury (8a) reported the m.p. 205° for this compound; our m.p. was 192-194° for the product obtained by either procedure A or procedure B.

Arylacetylmalononitriles.

p-Methoxyphenylacetylmalononitrile and *p*-chlorophenylacetylmalononitrile were prepared by procedure B as described in the preceeding section, but were obtained as oils rather than solids following acidification of the intermediate sodium salts with sulfuric acid. The oils were taken up by three extractions with 100-ml. portions of ether and the dried (sodium sulfate) extracts were concentrated by evaporation to yield the products in the form of oils, which were first methylated, then converted into 5-amino-4-cyanopyrazoles by reaction with hydrazine, as described below.

Aryl- and Benzylmethoxymethylenemalononitriles.

Two similar procedures were employed. Procedure A was that of A. Dornow and E. Schleese (8c); procedure B was a modification using a smaller volume of dioxane and an extraction step which gave better results with products which did not separate readily in solid form upon dilution of the reaction mixture with water.

Procedure A.

The acylmalononitrile (0.03 mole) was treated with 10 ml. of dimethylsulfate in a mixture prepared from 75 ml. of dioxane, 8 ml. of water and 10 g. of sodium bicarbonate. The mixture was heated for 2 hours at 80-90° on a water-bath, and then poured into a large volume of water to dissolve unreacted sodium bicarbonate. The solid that separated was filtered, washed with water and recrystallized from methanol.

Procedure B.

The acylmalononitrile (0.075 mole) was dissolved in a mixture of 120 ml. of dioxane and 20 ml. of water and treated with 50 ml. of dimethylsulfate and 50 g. of sodium bicarbonate. The mixture was heated on a water-bath at 80-90° for 2 hours. It was then cooled and water (600 ml.) was added. The mixture was extracted with ether (4 x 150 ml.), and the ether extracts washed with water and dried (sodium sulfate). The solvent was evaporated and the solid residue was crystallized from methanol.

The previously known compounds *p*-chlorophenylmethoxymethylenemalononitrile (m.p. 123°, reference 8a) (62.7% yield) and phenylmethoxymethylenemalononitrile (m.p. 93-94°, reference 8c) (49.7% yield) were prepared by procedure B and *p*-methoxyphenylmethoxymethylenemalononitrile (m.p. 73°, reference 8a) (35% yield) was prepared by procedure A. The new derivatives 3,4-methylenedioxyphenylmethoxymethylenemalononitrile, *p*-methoxybenzylmethoxymethylenemalononitrile, and *p*-chlorobenzylmethoxymethylenemalononitrile, prepared by procedure B, were obtained only as oils from ether extracts of the diluted reaction mixtures. They were converted without purification into corresponding 5-amino-4-cyanopyrazoles by reaction with methyl hydrazine or hydrazine hydrate. *p*-Tolylmethoxymethylenemalononitrile, another new compound obtained by procedure A, was fully characterized.

p-Tolylmethoxymethylenemalononitrile.

From *p*-toluoylmalononitrile (5.29 g., 0.03 mole) the yield was 2.8 g. (47%); white crystals, m.p. 102-103.5° (from methanol); ir: 4.46 (C≡N), 6.20, 6.30, 6.42, 6.58, 7.40, 7.74, 8.08, 8.58, 8.68, 10.30, 10.78, 12.08, 13.62, 14.54. Nmr (deuteriochloroform): δ 2.47 (s, 3, CH_3), 3.95 (s, 3, OCH_3), 7.48 (s, 4, aromatic).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.73; H, 5.05; N, 14.14. Found: C, 72.63; H, 5.11; N, 14.10.

3-(Aryl or benzyl)-5-amino-4-cyanopyrazoles.

The aryl or benzyl-substituted methoxymethylenemalononitriles were dissolved in ethanol (0.01 mole in 30 ml. of ethanol). An equimolar amount of methylhydrazine or β-hydroxyethylhydrazine was added and the solution was refluxed for 90 to 120 minutes. The solvent was then removed by evaporation and water was added to the residue. The solid product was collected by filtration and recrystallized from aqueous ethanol or a methylene chloride-petroleum ether mixture. Reactions of the substituted methoxymethylenemalononitriles with hydrazine were carried out without added solvent in the following manner:

To the aryl or benzyl substituted methoxymethylenemalononitrile was added a ten-fold molar quantity of hydrazine hydrate (85%) and the mixture was heated for 1 hour on a steam bath. It was then cooled and water (*ca.* 40 ml. for each 0.01 mole of methoxymethylenemalononitrile derivative) was added. The solid that precipitated was collected by filtration and purified by recrystallization. Data on these products are compiled in Table V. Yields quoted for 3-aryl derivatives are based on the methoxymethylene intermediate, except where otherwise indicated (13).

1- and/or 3-Substituted-4,6-diaminopyrazolo[3,4-*d*]pyrimidines.

Procedure A. Guanidine Carbonate Fusion.

The 5-amino-4-cyanopyrazole derivative (0.1 mole) was mixed with 0.15 to 0.2 mole of guanidine carbonate by grinding these reactants together in a mortar. The mixture was placed in a stoppered side-arm test-tube supported in an oil bath and maintained under slightly reduced pressure (*ca.* 120 mm.) while the temperature was raised and usually held 10-30° above the melting point of the pyrazole derivative. Heating was continued for the 2 to 3 hours required for the bubbling of the mixture to subside almost completely, and for the mass to resolidify to a large extent. The mixture was then cooled, powdered, washed with water and crystallized from water, dimethylformamide-water mixtures or aqueous ethanol.

Procedure B. Reaction with Guanidine Carbonate in Triethanolamine.

The 5-amino-4-cyanopyrazole (0.01 mole) was ground in a mortar with 0.0175 mole of guanidine carbonate. The mixture was placed in the apparatus described above for procedure A and 5 to 10 ml. of triethanolamine was added. The mixture was then heated under somewhat reduced pressure (*ca.* 120 mm.) in an oil bath. At *ca.* 160° a brisk evolution of gases began. The temperature was raised to *ca.* 210° over a period of 30 minutes, then held at 200-210° for 2.5 hours. The mixture was then cooled and warm water was added. The precipitated products were recrystallized from dimethylformamide-water mixtures.

Results for these preparations are compiled in Table I (14).

4-Aminopyrazolo[3,4-*d*]pyrimidines.

The 5-amino-4-cyanopyrazole (1.0 g.) was added to 10 ml. of formamide. The mixture was refluxed for 2-3 hours, then poured into water. The solid that separated was collected by filtration and recrystallized, usually from ethanol. Results are compiled in Table II.

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(10) Microanalyses are by M-H-W Laboratories, Garden City, Michigan. Melting points were determined with a Mel-Temp apparatus in capillary tubes and are corrected. Nuclear magnetic resonance spectra were determined on a Perkin-Elmer Hitachi R-20 instrument. Solutions in trifluoroacetic acid-deuteriochloroform mixtures were used except where otherwise indicated by TFA (trifluoroacetic acid only) or deuteriochloroform (deuteriochloroform only). Nmr signals are described by the symbols s for singlet, d for doublet, t for triplet, q for quartet, br for broad signal, and m for complex multiplet. For quartets of the AB type (pairs of doublets) the chemical shift values are given for the outer signals of the quartet, together with the coupling constant. Infrared spectra (only more prominent bands are given) were obtained from Nujol mulls with a Perkin-Elmer model 237B spectrophotometer.

(11) Ultraviolet spectra (0.1*N* sodium hydroxide in 95% ethanol)

showed maxima near 233 nm. For the 1-(3-chloro-4-methylphenyl) derivative λ max = 232 nm, log ε = 4.418. All spectra taken with Perkin-Elmer Model 202.)

(12) Ultraviolet spectra (0.1*N* sodium hydroxide in 95% ethanol) were very similar to those of 3-unsubstituted derivatives. For the 1-*p*-chlorophenyl derivative λ max = 233 nm, log ε = 4.437.

(13) Ultraviolet spectra of 3-(substituted benzyl) derivatives showed a single maximum at *ca.* 227 nm. For the 3-(*p*-chlorobenzyl) derivative λ max = 228 nm, log ε = 4.1086 (0.1*N* sodium hydroxide in 95% ethanol). 3-Aryl derivatives had two maxima. For the 1-methyl-3-*p*-tolyl derivative λ max = 233 nm (log ε = 4.203) and 257 nm (log ε = 4.186).

(14) Ultraviolet spectra of most of these 4,6-diaminopyrazolo[3,4-*d*]pyrimidine derivatives in 0.1*N* aqueous sodium hydroxide showed three maxima at 217-221 nm, 241-248 nm and 268-278 nm. For the 3-(*p*-chlorophenyl)-1-methyl derivative λ max = 218 nm (log ε = 4.600), 241 nm (log ε = 4.362) and 268 nm (log ε = 4.279).