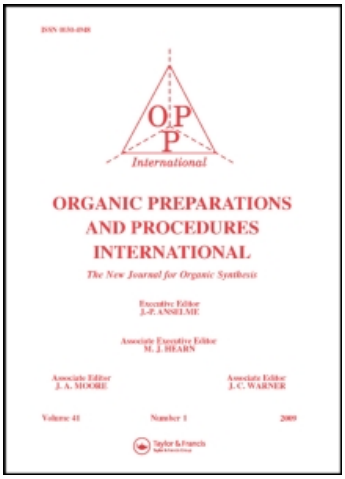

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4-AMINOPYRAZOLO[3,4-d]PYRIMIDINES

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4-AMINOPYRAZOLO[3,4-d]PYRIMIDINES

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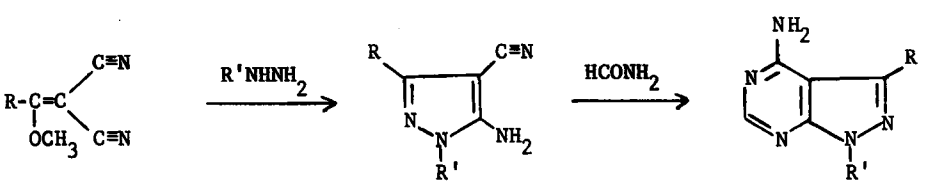
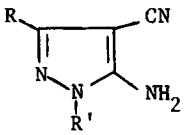
Interest in the derivatives of 4-aminopyrazolo[3,4-d]pyrimidine (3) has continued because of the activity of the parent compound (3, R = R' = H) against a wide spectrum of tumors.[1] More recently, several new derivatives of 4-aminopyrazolo[3,4-d]pyrimidine have been prepared and found to possess antitumor[2,3] and antimicrobial[4] activities. We recently described the preparation of several 4,6-diamino- and 4-aminopyrazolo[3,4-d] pyrimidine derivatives with variations in substitution at the 1- and 3- positions.[5] In this paper, we report the preparation of seven new 4-aminopyrazolo-[3,4-d]pyrimidine derivatives (3) which were obtained by the reaction of 5-amino-4-cyanopyrazoles (2) with formamide. The intermediate 5-amino-4-cyanopyrazoles (2) were obtained by the reaction of methoxymethylenemalononitrile derivatives (1) with hydrazine, methylhydrazine or arylhydrazines (Scheme I). Results are recorded in Tables I and II.



1 2 3

SCHEME I

TABLE I. 5-Amino-4-cyanopyrazoles (2)



R	R'	mp. (°C)	Yield[a] (%)	Formula	Analysis[d] Calcd. (Found) C	H	N
4-CH_3O-C_6H_4	H	180-181	62(A)	$C_{11}H_{10}N_4O$[b]	61.67 (61.49)	4.71 (4.55)	26.16 (26.03)
4-CH_3-C_6H_4	CH_3	161-162	78(C)	$C_{12}H_{12}N_4$	67.90 (67.97)	5.70 (5.50)	26.40 (26.17)
4-CH_3-C_6H_4	4-Cl-C_6H_4	174-175	45(B)	$C_{17}H_{13}ClN_4$[c]	66.13 (66.35)	4.21 (4.37)	18.15 (18.15)
4-Cl-C_6H_4	2,4-$Cl_2C_6H_3$	210-211	36.5(C)	$C_{16}H_9Cl_3N_4 \cdot 1.5\ H_2O$	49.16 (49.80)	3.07 (2.96)	14.34 (14.50)

a) A indicates crystallization from water; B from ethanol; C from aqueous ethanol.

b) Ir (Nujol): 2.96, 3.00, 3.12 (NH), 4.46 (C≡N), 6.08, 6.18, 6.30, 6.50, 6.60, 6.69, 7.75, 7.98, 8.50, 9.30, 9.74, 10.40, 12.05, 13.00, 13.56 μm; NMR ($CDCl_3$-trifluoroacetic acid (TFA)); δ 3.98 (s, 3, $\underline{OCH_3}$); 7.10-7.93 (q, J = 9Hz, 4, aromatic).

c) Ir (Nujol): 2.82, 2.95 (NH), 4.48 (C≡N), 6.16, 6.42, 9.26, 10.00, 10.24, 12.14, 13.3, 12.28, 13.78 μm. NMR ($CDCl_3$-TFA); δ 2.47 (s, 3, $\underline{CH_3}$); 7.20-7.87 (m, 8, aromatic).

d) Microanalyses by M-H-W Laboratories, Phoenix, Arizona.

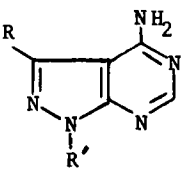
EXPERIMENTAL

5-Amino-4-cyanopyrazoles (2). - Compounds in which R'=H or CH_3 were obtained essentially by the methods described[5] for similar compounds. 1,3-Diaryl-5-amino-4-cyanopyrazoles were obtained as follows.

An arylhydrazine hydrochloride was added to an equimolar quantity of 0.5 molar ethanolic sodium ethoxide. An equimolar amount of arylmethoxymethylenemalononitrile[5] was then added in small portions and the mixture was refluxed for 60-90 minutes on a steam bath. The mixture was then cooled and the product was collected by filtration. In the case of 5-amino-3-(p-chlorophenyl)-1-(2,4-dichlorophenyl)pyrazole-4-carbonitrile

the product did not separate on cooling. The solution in this case was evaporated to dryness and water was added to the residual paste to obtain a reddish solid. The crude samples were washed with petroleum ether (bp 30-60°C) to remove a red color and purified by crystallization from the solvents indicated in Table I.

TABLE II. 4-Aminopyrazolo[3,4-d]pyrimidines (3)



R	R'	mp. (°C)	Yield[a] (%)	Formula	Analysis[d] Calcd. (Found) C	H	N
4-$CH_3OC_6H_4$	H	304-305	40.4(A)	$C_{12}H_{11}N_5O$	59.74 (59.75)	4.60 (4.36)	29.03 (29.23)
4-$CH_3OC_6H_4CH_2$	H	266	65(B)	$C_{13}H_{13}N_5O$[b]	61.16 (60.90)	5.13 (4.88)	27.44 (27.49)
CH_3	3-Cl-4-$CH_3C_6H_3$	218-219	66(A)	$C_{13}H_{12}ClN_5$	57.04 (56.86)	4.39 (4.20)	25.59 (25.57)
CH_3	4-Cl-2-$CH_3C_6H_3$	256-257	66(B)	$C_{13}H_{12}ClN_5$	57.04 (56.99)	4.39 (4.19)	25.59 (25.70)
4-$CH_3C_6H_4$	CH_3	183-184	61(A)	$C_{13}H_{13}N_5$	65.25 (65.22)	5.48 (5.50)	29.27 (29.28)
4-$CH_3C_6H_4$	4-ClC_6H_4	288-289	64(B)	$C_{18}H_{14}ClN_5$[c]	64.38 (64.21)	4.17 (4.22)	20.86 (20.84)
4-ClC_6H_4	2,4-$Cl_2C_6H_3$	237-238	67(B)	$C_{17}H_{10}Cl_3N_5$	52.24 (52.48)	2.56 (2.47)	17.92 (17.80)

a) A indicates crystallization from aqueous ethanol; B, from absolute ethanol.

b) Ir (Nujol): 2.86, 2.98, 6.00, 6.28, 6.60, 7.60, 7.80, 8.00, 9.70, 12.45, 12.70, 13.20 μm. NMR ($CDCl_3$-TFA): δ 3.95 (s, 3, OCH_3); 4.50 (s, 3, $\underline{CH_2}$); 6.97-7.37 (q, J = 9Hz, 4, aromatic); 8.63 (s, 1, H at 6-position).

c) Ir (Nujol): 2.86, 3.02 (NH), 6.02, 6.30, 6.40, 6.65, 7.64, 9.18, 10.10, 11.90, 12.52 μm. NMR ($CDCl_3$-TFA); δ 2.50 (s, 3, $\underline{CH_3}$); 7.40-7.80 (m, 8, aromatic); 8.54 (s, 1, H at 6-position).

4-Aminopyrazolo[3,4-d]pyrimidines (3). - The 5-amino-4-cyanopyrazole (1.0 g was added to 10 ml of formamide. The mixture was refluxed for 2 or 3 hours then poured into water. The solid that precipitated was collected by filtration and purified by crystallization from ethanol or aqueous ethanol. Results are recorded in Table II.

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