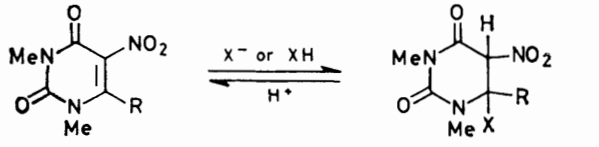
Pyrimidine Derivatives and Related Compounds. Part 41.[1] Reactions of 1,3,6-Trimethyl-5-nitrouracil and its 6-Bromomethyl Analogue with Amines and Hydrazines. Synthesis of Pyrazolo[4,3-*d*]pyrimidine *N*-Oxides and their Ring Expansion to Pyrimido[5,4-*d*]pyrimidines[2]

By **Kosaku Hirota,* Yoshihiro Yamada, Tetsuji Asao,** and **Shigeo Senda,** Giful College of Pharmacy, Mitahora-higashi, Gifu 502, Japan

Reactions of 1,3,6-trimethyl-5-nitrouracil (1) and 6-bromomethyl-1,3-dimethyl-5-nitrouracil (4) with amines and hydrazines have been studied with the aim of synthesising fused-ring pyrimidines. Treatment of compound (4) with primary amines afforded 2-substituted pyrazolo[4.3-*d*]pyrimidine 1-oxides (6a—l). Of these, compounds (6h—l) were converted into pyrimido[5,4-*d*]pyrimidines (11) by treatment with sodium ethoxide. Although treatment of compound (1) with hydrazines caused the known ring transformation giving pyrazolones (2a and b), a new type of denitration reaction was found when compound (4) reacted with hydrazines yielding 6-hydrazonomethyl-1,3-dimethyluracils (15a and b). Treatment of the 6-(substituted methyl)-1,3-dimethyl-5-nitrouracils (13b—d) and (14) [prepared from (4)] with hydrazines also gave (15a and b). Mechanisms for the formation of compounds (6), (11), and (15) are discussed.

REACTIONS of uracil derivatives with various nucleophiles have been studied extensively in connection with the biosynthesis of thymidylate,[3] the chemical modification of nucleic acids,[4] and ring transformation reactions for the synthesis of heterocycles.[5] 5-Nitrouracils are particularly reactive, undergoing nucleophilic attack at the 6-position. Nucleophiles such as ^-OEt,[6,7] ^-OH,[7] SO_3^{2-},[8] and ^-CN [9] add across the 5,6-double bond to form 5,6-dihydrouracils (Scheme 1). On the other hand, 6-



R = H or Me

X = OH, OEt, SO_3^-, NHOH, NH_2 NH, or CN

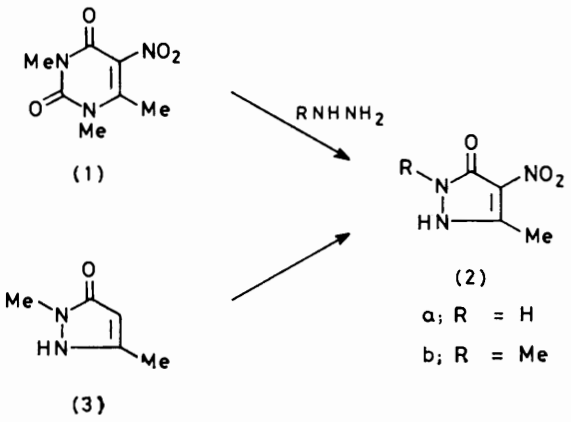
SCHEME 1

methyl-5-nitrouracils are useful intermediates for synthesizing fused-ring pyrimidines, *e.g.* pyrrolo[3,2-*d*]-pyrimidines [10] and pyrazolo[4,3-*d*]pyrimidines.[11]

In a study of the reaction of 1,3,6-trimethyl-5-nitrouracil (1) with amines and hydrazines with a view to developing new synthetic routes to fused-ring pyrimidines, we have found that 6-bromomethyl-1,3-dimethyl-5-nitrouracil (4), easily derived from (1), reacts with primary amines to afford pyrazolo[4,3-*d*]pyrimidine *N*-oxides (6) and with hydrazines to undergo a novel denitration reaction.

RESULTS AND DISCUSSION

First the stability of compound (1) toward amines and hydrazines was investigated.† On treatment with butylamine under drastic conditions (sealed tube at 200 °C), essentially no reaction took place and most of (1) was recovered. However treatment of a solution of (1) in propan-2-ol with hydrazine hydrate caused ring contraction to yield 1,2-dihydro-5-methyl-4-nitropyrazol-3-one (2a). Similarly, 1,2-dihydro-2,5-dimethyl-4-nitropyrazol-3-one (2b) was obtained by treatment



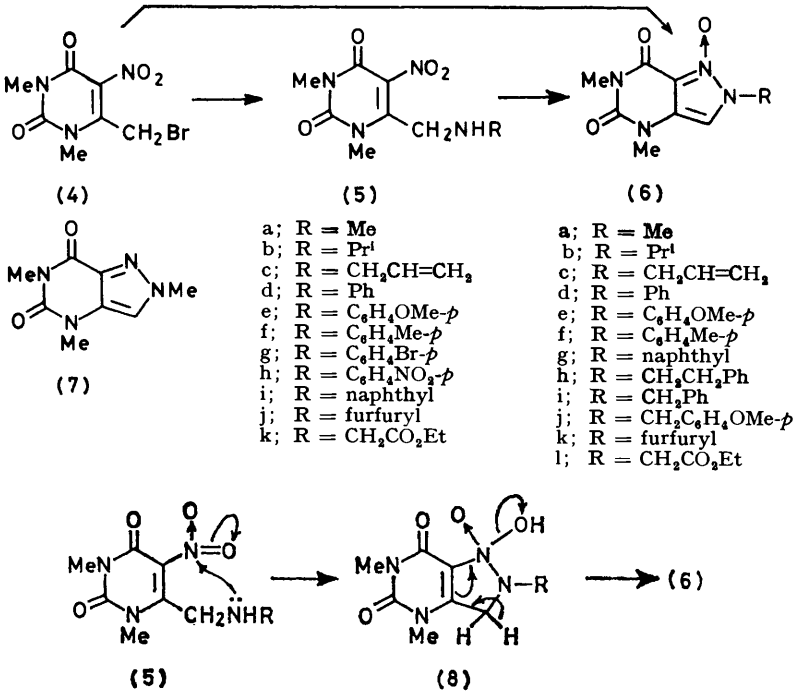
SCHEME 2

with methylhydrazine. The structure of (2b) was confirmed by comparison with a sample obtained by nitration of 1,2-dihydro-2,5-dimethylpyrazol-3(3*H*)-one (3).[12] Such ring transformations have been investigated previously in detail.[13]

6-Bromomethyl-1,3-dimethyl-5-nitrouracil (4) was then studied, since it was expected to be highly reactive towards amines. Indeed, reactions of (4) with primary amines, such as alkylamines, phenethylamine, benzylamines, and furfurylamine, in refluxing ethanol caused direct ring closure giving the corresponding 2-substituted 4,6-dimethyl-2*H*-pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,-6*H*)-dione 1-oxides (6a—c) and (6h—l).[11,14,15] Catalytic reduction of (6a) gave the deoxygenation product (7), identical with an authentic sample.[15] Careful treatment of (4) in ethyl acetate with the same amines as mentioned above with cooling in an ice-bath afforded the cor-

† Fox and his co-workers report in a footnote to ref. 7 that the reaction of 1,3-dimethyl-5-nitrouracil with amines and hydrazine furnishes the corresponding 5,6-dihydro-adducts and that these amine adducts are hydrolysed easily by traces of water to give back the starting material.

responding 6-(substituted amino)methyl-1,3-dimethyl-5-nitrouracils (5a—c) and (5j). These intermediates were then thermally cyclized to the corresponding pyrazolo-[4,3-*d*]pyrimidines (6a—c) and (6k). The intermediates obtained in the reactions with benzylamine, *p*-methylbenzylamine, and phenethylamine were isolated in crude form, but on attempted purification cyclized directly to the pyrazolo[4,3-*d*]pyrimidines (6h—j).



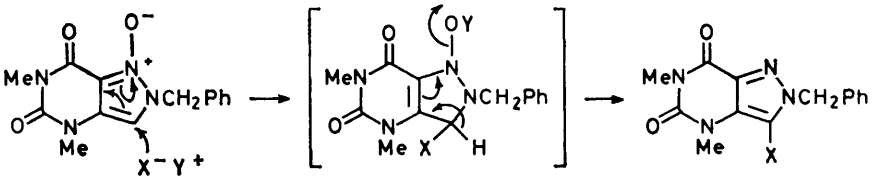
SCHEME 3

The proposed mechanism for this reaction is shown in Scheme 3. An initial displacement of the bromo-group by the primary amine gives rise to the intermediate (5), which cyclizes to (8) and on further dehydration gives (6).

Treatment of compound (4) with arylamines in ethyl acetate at room temperature gave the 6-arylamino-methyl-5-nitrouracils (5d—i). However, refluxing (5d—i) in ethanol did not afford the expected pyrazolo-[4,3-*d*]pyrimidines; only the starting materials were recovered. However when (5d—f) and (5i) were treated with triethylamine in methanol at room temperature, ring closure occurred to give the 2-aryl derivatives (6d—g). These results suggest that an arylamino-group is not so reactive towards the nitro-group as an alkylamino-group. Similar treatment of (5g) and (5h), which possess much more weakly basic arylamino-groups, did not give the corresponding pyrazolo[4,3-*d*]pyrimidines.

An amino-acid ester could also be used in these cyclization reactions. Thus, glycine ethyl ester hydrochloride with (4) in absolute ethanol at room temperature in the presence of sodium ethoxide gave the intermediate (5k), treatment of which with triethylamine in refluxing ethanol afforded the pyrazolo[4,3-*d*]pyrimidine (6l) in which N-2 is derived from the amino-acid.

The reactivity of these *N*-oxides was then investi-



SCHEME 4

gated.[16] Reaction of the 2-benzylpyrazolo[4,3-*d*]-pyrimidine 1-oxide (6i) with acetic anhydride or acetyl chloride at 80 °C gave the 3-acetoxy- (9a) or the 3-chloro-2-benzylpyrazolo[4,3-*d*]pyrimidine (9b), respectively. Compound (9b) was also prepared by treatment of (6i) with phosphoryl chloride at reflux temperature.

TABLE 1

6-(Substituted amino)methyl-1,3-dimethyl-5-nitrouracils (5)

Compound	Method	Reaction time (h)	Yield (%)	Recryst. solvent	M.p. (°C)	$\nu_{max.}$/cm^{-1} (NH)
(5a)	A	1.5	34	Et_2O	99—100	3 340
(5b)	A	3	98	Et_2O	88	3 340
(5c)	A	2	91	Et_2O	82—83	3 340
(5d)	B	4	79	EtOH	162 (decomp.)	3 340
(5e)	B	5	65	MeOH	174—176 (decomp.)	3 360
(5f)	B	5	80	MeOH	165—167 (decomp.)	3 350
(5g)	B	6	76	MeOH	163—164	3 350
(5h)	B	6	87 [a]	EtOH	125—127	3 360
(5i)	B	6	29	MeOH	186 (decomp.)	3 420
(5j)	A	4	78	Et_2O	79—80	3 340
(5k)	C	1	75	EtOH	130—131	3 340

[a] Isolated as the hydrobromide salt.

Treatment of compounds (6i—k), bearing an active methylene group attached to N-2, with sodium ethoxide gave the corresponding pyrimido[5,4-*d*]pyrimidines (11a—c).[17] When the 1-oxide (6l) was treated under the same conditions, the ring transformation product was not obtained. However, heating (6l) in diethylene glycol dimethyl ether (diglyme) with sodium hydride afforded the expected product (11d). The structures of the products (11a—d) were supported by elemental analyses and spectroscopic data.

A reasonable mechanism for the transformation of (6) into (11) *via* an azahexatriene (12) [18] may be formulated as shown in Scheme 5. This mechanism is similar to the one proposed for the conversion of 3-amino-1-benzylindazole into 4-amino-2-phenylquinazoline in the presence of sodium hydride.[19]

Treatment of secondary amines such as dimethylamine, morpholine, and *N*-methylaniline with (4) afforded the corresponding bromine substitution products (13a—c) in high yields.

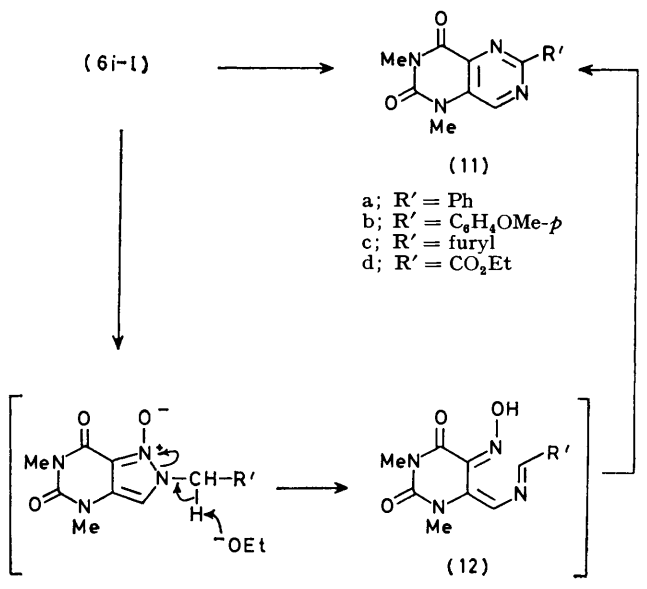
The reaction of (4) with hydrazine hydrate was complex; no product was isolated. However, when (4) was treated with an excess of methylhydrazine in ethyl acetate cooled in ice, complete transformation of the starting material was achieved, but the isolated product was the denitro-hydrazone (15b) (83% yield), identical with an authentic sample prepared by methylation of 6-methylhydrazonouracil[20] with dimethyl sulphate. Similar treatment of (4) with 2 equiv. of methylhydrazine gave 1,3-dimethyl-6-(α-methylhydrazino)methyl-5-nitrouracil (14), identified on the basis of the formation of a hydrazone with benzaldehyde.

TABLE 2

Preparation and spectral data of 2-substituted 4,6-dimethyl-2*H*-pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione 1-oxides (6)

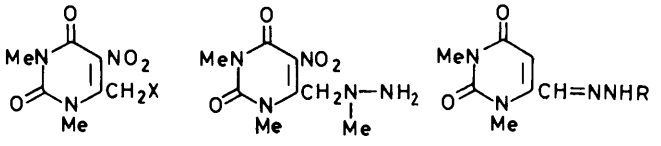
Compound	From (4) Method [a,b]	From (4) Yield (%)	From (5) Method [a,b]	From (5) Yield (%)	M.p. (°C) (decomp.)	$\lambda_{max.}$(EtOH)/nm (ε)	δ(H-3)	δ(NMe)
(6a)	A (4)	23	B (12)	55	265—266 (MeOH)	221 (18 100), 269 (6 300), 327 (5 100)	7.48 [d]	3.51 3.56
(6b)	A (4)	19	B (16)	63	183—184 (Pr^{i}OH)	221 (19 600), 270 (7 000), 329 (5 000)	6.58 [e]	3.36 3.38
(6c)	A (4)	53	B (24)	81	216—217 (Pr^{i}OH)	221 (18 100), 270 (6 900), 329 (4 900)	7.15 [d]	3.54 3.60
(6d)			C (2)	49	163—164 (EtOH)	221 (19 500), 240 (19 500), 277sh (11 900), 343 (4 700)	*f*, *g*	3.59 3.66
(6e)			C (12)	72	160 (MeOH)	222 (23 600), 233sh (20 500), 283 (14 200), 340 (5 400)	*f*, *g*	3.62 3.66
(6f)			C (2)	61	166—167 (MeOH)	220 (21 700), 242 (19 100), 262sh (17 100), 279sh (13 100), 343 (4 900)	7.63 [g]	3.58 3.65
(6g)			C (12)	57	170—175 (MeOH)	221 (27 900), 287 (12 300), 330sh (4 800)	*f*, *g*	3.62 3.66
(6h)	A (6)	61			219—220 (EtOH)	222 (21 000), 230sh (21 000), 271 (7 900), 330 (4 800)	6.22 [e]	3.28 3.36
(6i)	A (4)	58			239—240 (MeOH)	221 (21 800), 233sh (20 600), 274 (8 100), 332 (4 900)	*d*, *f*	3.52 3.52
(6j)	A (6)	62			225—226 (MeOH)	229 (27 600), 275 (10 000), 332 (4 800)	7.43 [d]	3.55 3.62
(6k)	A (4)	59	B (16)	65	219—220 (MeOH)	221 (25 900), 274 (8 000), 331 (5 000)	7.43 [d]	3.57 3.63
(6l)			D (0.5)	69	227—229 (MeOH)	223 (19 600), 230sh (18 400), 272 (7 300), 332 (4 900)	7.62 [g]	3.57 3.63

[a] See Experimental section. [b] Reaction time (h) in parentheses. [c] Recrystallization solvent in parentheses. [d] CF_3CO_2D solutions. [e] $CDCl_3$ solutions. [f] Obscured by aromatic signals. [g] CF_3CO_2H solutions.



SCHEME 5

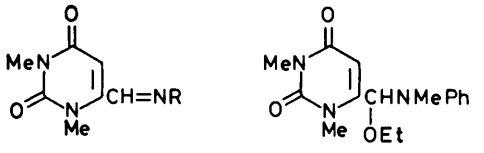
Further treatment of (14) with methylhydrazine caused loss of the nitro-group to give (15b). Conversion of (14) into the crossed product (15a) occurred in 76% yield on refluxing in methanol with hydrazine hydrate. The reaction of (14) with phenylhydrazine did not yield the crossed product.



(13) (14) (15)

a; X = NMe_2
b; X = morpholino
c; X = NMePh
d; X = OCOMe

a; R = H
b; R = Me

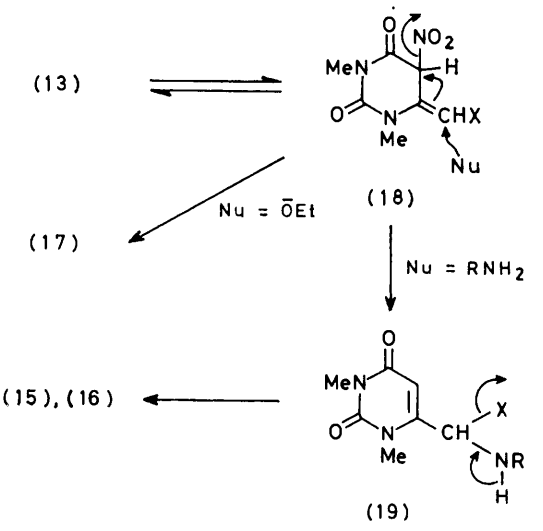


(16) (17)

a; R = Ph
b; R = NHPh

In order to elucidate the mode of loss of the nitro-group, 6-(substituted methyl)-1,3-dimethyl-5-nitrouracils (13) were treated with hydrazines and with aniline. Reactions with hydrazine hydrate and with methylhydrazine in refluxing methanol smoothly led to (15a) and (15b), respectively. Similar treatment of (13c) or (13d) [prepared by reaction of (4) with sodium acetate] with hydrazine hydrate and with methylhydrazine also yielded (15a) or (15b). Furthermore, reaction of (13c) with aniline in the presence of triethylamine gave 6-phenyliminomethyl-1,3-dimethyluracil (16a). Similar reaction of (13c) with phenylhydrazine in the presence of triethylamine afforded the phenylhydrazone (16b). It is noteworthy that the denitration is caused even by aniline; thus a reductive denitration mechanism can be eliminated.

These denitrations are apparently similar to the



SCHEME 6

abnormal nucleophilic substitution reported previously.[21] We tentatively suggest the mechanism outlined in Scheme 6. Compound (13) in the presence of base gives the tautomer (18) [trapped in one instance (13c) by refluxing in ethanol in the presence of triethylamine to give the adduct (17) *via* elimination of nitrous acid]. The tautomer (18) could undergo nucleophilic addition by hydrazines or aniline to give (19), from which (15) or (16) could be formed by elimination of HX.

Although some denitration reactions of 5-nitropyrimidines have been reported,[22] similar ones in the pyrimidine series have not been described hitherto.

EXPERIMENTAL

M.p.s were determined on a Yanagimoto hot-stage apparatus. ^{1}H N.m.r. spectra were recorded on a Hitachi Perkin-Elmer R-20B 60 MHz spectrometer with tetramethylsilane as internal standard. I.r. spectra were obtained with a Hitachi 215 instrument for KBr pellets. U.v. spectra were recorded for solutions in EtOH on a Hitachi 323 spectrophotometer.

1,2-*Dihydro*-5-*methyl*-4-*nitropyrazol*-3-*one* (2a).—A mixture of the 5-nitrouracil (1) (1 g, 0.005 mol) and hydrazine hydrate (2.5 g, 0.05 mol) in propan-2-ol (6 ml) was heated to reflux for 1 h. The solvent was evaporated off *in vacuo* and to the residue was added hydrochloric acid (10%; 10 ml). The precipitate was filtered off and dried to give the *pyrazolone* (2a) (0.26 g, 36%). Recrystallization from aqueous dimethylformamide gave prisms, m.p. 276 °C (decomp.) (Found: C, 33.55; H, 3.5; N, 29.45. $C_4H_5N_3O_3$ requires C, 33.55; H, 3.5; N, 29.35%); $\nu_{max.}$ 1 630 cm^{-1} (C=O); $\lambda_{max.}$ 283 nm (ε 7 000); δ[$(CD_3)_2SO$] 2.46 (3 H, s, Me) and 9.10 (2 H, br, NH).

1,2-*Dihydro*-2,5-*dimethyl*-4-*nitropyrazol*-3-*one* (2b).—(*a*) A

mixture of the 5-nitrouracil (1) (1 g, 0.005 mol) and methylhydrazine (2.3 g, 0.05 mol) in propan-2-ol (6 ml) was heated to reflux for 45 min. The solvent was evaporated off *in vacuo* and to the residue was added hydrochloric acid (10%; 10 ml). The precipitate was filtered off and dried to give the *pyrazolone* (2b) (0.4 g, 55%). Recrystallization from water gave yellow needles, m.p. 157—158 °C (decomp.) (Found: C, 38.1; H, 4.5; N, 26.55. $C_5H_7N_3O_3$ requires C, 38.2; H, 4.5; N, 26.75%); $\nu_{max.}$ 1 680 cm^{-1} (C=O); $\lambda_{max.}$ 290 nm (ε 7 300); δ[$(CD_3)_2SO$] 2.33 (3 H, s, Me) and 3.50 (3 H, s, NMe).

(*b*) To a stirred mixture of fuming nitric acid (2 ml) and concentrated sulphuric acid (2 ml) was added in portions 1,2-dihydro-2,5-dimethylpyrazol-3-one (3) [12] (1 g, 0.009 mol) below 0 °C with cooling in an ice–salt bath. When all of (3) had dissolved, the mixture was poured over ice. The resulting precipitate was separated by filtration, washed with water, and dried to give the pyrazolone (2b) (0.6 g, 43%).

6-(*Substituted amino*)*methyl*-1,3-*dimethyl*-5-*nitrouracils* (5a—l) (*Table* 1).—*General procedure. Method A.* To a solution of the 5-nitrouracil (4) (1.4 g, 0.005 mol) in ethyl acetate (20 ml) was added dropwise an amine (0.01 mol) with cooling in an ice-bath. After the reaction was complete the mixture was filtered and the filtrate was evaporated *in vacuo* at room temperature. To the residue was added water and the precipitate was collected by filtration and dried.

Method B. To a solution of the 5-nitrouracil (4) (1.4 g, 0.005 mol) in ethyl acetate (20 ml) was added an arylamine (0.01 mol) at room temperature. After the reaction was complete the mixture was filtered and the filtrate was evaporated *in vacuo*. To the residue was added ether and the precipitate was filtered off, washed with water, and dried.

Method C. To a stirred suspension of the 5-nitrouracil (4) (1.4 g, 0.005 mol) and glycine ethyl ester hydrochloride (1.4 g, 0.01 mol) in absolute ethanol (30 ml) was added a solution of sodium ethoxide [from sodium (0.23 g, 0.01 mol)] in ethanol (5 ml). The mixture was stirred at room temperature for 2 h and the solvent was evaporated off *in vacuo*. To the residue was added water and the precipitate was separated by filtration and dried.

2-*Substituted* 1,3-*Dimethyl*-2H-*pyrazolo*[4,3-d]*pyrimidine*-5,7(4H,6H)-*dione* 1-*Oxides* (6a—l) (*Table* 2).—*General procedure. Method A.* A mixture of the 5-nitrouracil (4) (0.7 g, 0.0025 mol) and an amine (0.005 mol) in ethanol (20 ml) was heated to reflux. After the reaction was complete, the mixture was kept at room temperature, and the resulting precipitate was collected by filtration. When methylamine was used as the amine, the mixture was heated in a stainless steel vessel at 80 °C for 4 h, and then the solvent was evaporated off *in vacuo* and the residue was washed with water, filtered, and dried.

Method B. A solution of the substituted aminomethyluracil (5) in ethanol (15 ml) was heated to reflux. After the reaction was complete, the mixture was kept at room temperature and the precipitate was collected by filtration.

Method C. To a stirred suspension of the 6-(substituted amino)methyluracil (5) (0.002 mol) in methanol (15 ml) was added triethylamine (1 ml) at room temperature. After the reaction was complete, the resulting precipitate was collected by filtration.

Method D. A mixture of the 6-(substituted amino)-methyluracil (5) (0.002 mol) and triethylamine (1 ml) in absolute ethanol (20 ml) was refluxed for 30 min. The mixture was kept at room temperature and the precipitate was separated by filtration.

2,4,6-*Trimethyl*-2H-*pyrazolo*[4,3-d]*pyrimidine*-5,7(4H,-6H)*dione* (7).—A mixture of the 1-oxide (6a) (0.2 g, 0.000 95 mol) and palladium on charcoal (0.3 g) in methanol (150 ml) was heated at 80 °C under a H_2 pressure of 50 lb in^{-2} for 4 h. To the mixture was added charcoal. Filtration and evaporation *in vacuo* left the *product* (7) (0.155 g, 84%). Recrystallization from methanol afforded needles, m.p. 265—266 °C. Compound (7) was identical (spectral data) with an authentic sample prepared by the method of Papesch *et al.*[15]

3-*Acetoxy*-2-*benzyl*-4,6-*dimethyl*-2H-*pyrazolo*[4,3-d]*pyrimidine*-5,7(4H,6H)-*dione* (9a).—The 1-oxide (6i) (0.3 g, 0.0011 mol) in acetic anhydride (8 ml) was heated at 80 °C for 1 h. The solvent was evaporated off *in vacuo*. The

TABLE 3

Elemental analyses of compounds (5a—k) and (6a—l)

Compd.	Formula	Calc. C	Calc. H	Calc. N	Found C	Found H	Found N
(5a)	$C_8H_{12}N_4O_4$	42.1	5.3	24.55	42.15	5.35	24.55
(5b)	$C_{10}H_{16}N_4O_4$	46.85	6.3	21.85	46.85	6.35	21.95
(5c)	$C_{10}H_{14}N_4O_4$	47.25	5.55	22.05	47.15	5.55	22.2
(5d)	$C_{13}H_{14}N_4O_4$	53.8	4.85	19.3	53.75	4.9	19.45
(5e)	$C_{14}H_{16}N_4O_5$	52.5	5.05	17.5	52.4	5.0	17.5
(5f)	$C_{14}H_{16}N_4O_4$	55.25	5.3	18.4	55.25	5.3	18.35
(5g)	$C_{13}H_{13}BrN_4O_4$	42.3	3.55	15.15	42.25	3.5	15.1
(5h)	$C_{13}H_{14}BrN_5O_6$	37.55	3.4	16.85	37.65	3.35	16.65
(5i)	$C_{17}H_{16}N_4O_4$	60.0	4.75	16.45	60.25	4.65	16.45
(5j)	$C_{12}H_{14}N_4O_5$	49.0	4.8	19.05	48.95	4.8	19.2
(5k)	$C_{11}H_{16}N_4O_6$	44.0	5.35	18.65	44.1	5.35	18.75
(6a)	$C_8H_{10}N_4O_3$	45.7	4.8	26.65	46.0	4.8	26.9
(6b)	$C_{10}H_{14}N_4O_3$	50.4	5.9	23.5	50.35	5.95	23.4
(6c)	$C_{10}H_{12}N_4O_3$	50.85	5.1	23.7	50.9	5.25	23.6
(6d)	$C_{12}H_{12}N_4O_3$	57.35	4.45	20.6	57.6	4.35	20.65
(6e)	$C_{14}H_{14}N_4O_4$	55.6	4.65	18.55	55.8	4.6	18.6
(6f)	$C_{14}H_{14}N_4O_3$	58.75	4.95	19.55	58.9	4.85	19.85
(6g)	$C_{17}H_{14}N_4O_3$	63.35	4.4	17.4	63.2	4.35	17.15
(6h)	$C_{15}H_{16}N_4O_3$	60.0	5.35	18.65	60.2	5.4	18.5
(6i)	$C_{14}H_{14}N_4O_3$	58.75	4.95	19.55	58.8	4.95	19.75
(6j)	$C_{15}H_{16}N_4O_4$	56.95	5.1	17.7	56.85	5.1	17.8
(6k)	$C_{12}H_{12}N_4O_4$	52.2	4.4	20.3	52.0	4.2	20.4
(6l)	$C_{11}H_{14}N_4O_5$	46.8	5.0	19.85	47.0	5.0	19.85

precipitate was washed with water and dried to give the *pyrazolopyrimidine* (9a) (0.3 g, 87%). Recrystallization from propan-2-ol afforded needles, m.p. 200—201 °C (Found: C, 58.2; H, 4.85; N, 17.1. $C_{16}H_{16}N_4O_4$ requires C, 58.52; H, 4.9; N, 17.05%); $\nu_{max.}$ 1 790, 1 710, and 1 600 cm^{-1} (C=O); $\lambda_{max.}$ 240sh and 293 nm (ε 8 200 and 5 100); δ($CDCl_3$) 2.21 (3 H, s, COMe), 3.32 (3 H, s, NMe), 3.40 (3 H, s, NMe), 5.24 (2 H, s, CH_2), and 7.22 (5 H, m, aromatic).

2-Benzyl-3-chloro-4,6-dimethyl-2H-pyrazolo[4,3-d]*pyrimidine-5,7(4H,6H)-dione* (9b).—(*a*) A mixture of the pyrazolopyrimidine (6i) (0.57 g, 0.002 mol) and acetyl chloride (0.16 g, 0.002 mol) in dimethylformamide (20 ml) was heated at 80 °C for 10 min. The solvent was evaporated off *in vacuo*. To the residue was added water and the precipitate was filtered off and dried to give the *pyrazolopyrimidine* (9b) (0.6 g, 96%). Recrystallization from propan-2-ol afforded needles, m.p. 130—132 °C (Found: C, 55.2; H, 4.25; N, 18.45. $C_{14}H_{13}ClN_4O_2$ requires C, 55.2; H, 4.3; N, 18.4%); $\nu_{max.}$ 1 720 and 1 670 cm^{-1} (C=O); $\lambda_{max.}$ 245sh and 295 nm (ε 6 900 and 5 200); δ($CDCl_3$) 3.43 (3 H, s, NMe), 3.62 (3 H, s, NMe), 5.46 (2 H, s, CH_2), and 7.31 (5 H, s, aromatic).

(*b*) The pyrazolopyrimidine (6i) (0.29 g, 0.001 mol) in phosphoryl chloride (10 ml) was refluxed for 5 min. The solvent was evaporated off *in vacuo*. To the residue was added water and the precipitate was filtered off and dried to give the pyrazolopyrimidine (9b) (0.15 g, 49%).

6-Substituted 1,3-Dimethylpyrimido[5,4-d]*pyrimidine-2,4-(1H,3H)-diones* (11a—c).—*General procedure*. A mixture of the pyrazolopyrimidine (6i), (6j), or (6k) (0.002 mol) and sodium ethoxide [from sodium (0.05 g, 0.002 mol) in absolute ethanol (50 ml)] was heated to reflux until the precipitate dissolved. The mixture was kept at room temperature and the precipitate which gradually separated was collected by filtration. Recrystallization from methanol afforded needles.

1,3-Dimethyl-6-phenylpyrimido[5,4-d]*pyrimidine-2,4(1H,-3H)-dione* (11a) (71%) had m.p. 263—264 °C (Found: C, 62.75; H, 4.5; N, 20.95. $C_{14}H_{12}N_4O_2$ requires C, 62.7; H, 4.5; N, 20.9%); $\nu_{max.}$ 1 720 and 1 670 cm^{-1} (C=O); $\lambda_{max.}$ 249sh, 282sh, 288, and 300sh nm (ε 14 600, 27 500, 28 000, and 18 100); δ(CF_3CO_2D) 3.75 (3 H, s, NMe), 3.88 (3 H, s, NMe), 8.05 (5 H, m, aromatic), and 9.55 (1 H, s, H-8); the *6-(4-methoxyphenyl) derivative* (11b) (50%) had m.p. 259—260 °C (Found: C, 60.3; H, 4.75; N, 18.7. $C_{15}H_{14}N_4O_3$ requires C, 60.4; H, 4.75; N, 18.8%); $\nu_{max.}$ 1 720 and 1 670 cm^{-1} (C=O); $\lambda_{max.}$ 223 and 301 nm (ε 14 100 and 37 400); δ(CF_3CO_2D) 3.71 (3 H, s, NMe), 3.82 (3 H, s, NMe), 4.00 (3 H, s, OMe), 7.75 (4 H, m, aromatic), and 9.36 (1 H, s, H-8); the *6-(2-furyl) derivative* (11c) (61%) had m.p. 298—299 °C (Found: C, 56.0; H, 3.85; N, 21.75. $C_{12}H_{10}N_4O_3$ requires C, 55.8; H, 3.9; N, 21.7%); $\nu_{max.}$ 1 720 and 1 660 cm^{-1} (C=O); $\lambda_{max.}$ 302 and 312sh nm (ε 33 000 and 28 300); δ(CF_3CO_2D) 3.70 (3 H, s, NMe), 3.83 (3 H, s, NMe), 6.75 (1 H, m, aromatic), 7.80 (2 H, m, aromatic), and 9.33 (1 H, s, C_8H).

6-Ethoxycarbonyl-1,3-dimethylpyrimido[5,4-d]*pyrimidine-2,4(1H,3H)-dione* (11d).—A mixture of the pyrazolopyrimidine (6l) (0.56 g, 0.002 mol) and 53% sodium hydride (0.11 g, 0.0024 mol) (previously washed with dry ether) in bis-(2-methoxyethyl) ether (15 ml) was refluxed under a stream of N_2 for 4 h. The mixture was kept at room temperature and the resulting precipitate was collected by filtration. The precipitate was dissolved in N-HCl and the solution was extracted with chloroform. The chloroform solution was dried and evaporated to give the *6-ethoxycarbonylpyrimidopyrimidine* (11d) (0.18 g, 34%). Recrystallization from ethanol gave needles, m.p. 202—203 °C (Found: C, 50.1; H, 4.65; N, 20.95. $C_{11}H_{12}N_4O_4$ requires C, 50.0; H, 4.6; N, 21.2%); $\nu_{max.}$ 1 720 and 1 680 cm^{-1} (C=O); $\lambda_{max.}$ 253sh and 274 nm (ε 10 700 and 13 200); δ[$(CD_3)_2SO$] 1.37 (3 H, t, *J* 7 Hz, CMe), 3.34 (3 H, s, NMe), 3.59 (3 H, s, NMe), 4.39 (2 H, q, *J* 7 Hz, CH_2C), and 9.29 (1 H, s, H-8).

6-Dimethylaminomethyl-1,3-dimethyl-5-nitrouracil (13a).—To a solution of the 5-nitrouracil (4) (1.4 g, 0.005 mol) in ethyl acetate (25 ml) was added dropwise a 35% ethanolic solution of dimethylamine (1.3 ml, 0.01 mol) with stirring in an ice-bath. After the reaction was complete, the mixture was filtered and the filtrate was evaporated *in vacuo*. To the residue was added water and the precipitate was collected by filtration and dried to give the *6-dimethylaminomethyluracil* (13a) (1.18 g, 97%). Recrystallization from ethanol afforded yellow needles, m.p. 116—118 °C (Found: C, 44.6; H, 5.85; N, 23.0. $C_9H_{14}N_4O_4$ requires C, 44.6; H, 5.85; N, 23.15%); $\nu_{max.}$ 1 720 and 1 670 cm^{-1} (C=O).

1,3-Dimethyl-6-morpholinomethyluracil (13b).—Similar procedures to those mentioned above using the 5-nitrouracil (4) and morpholine afforded the *6-morpholinomethyluracil* (13b) in 81% yield. Recrystallization from propan-2-ol afforded yellow needles, m.p. 161—162 °C (Found: C, 46.45; H, 5.7; N, 19.65. $C_{11}H_{14}N_4O_5$ requires C, 46.45; H, 5.65; N, 19.7%); $\nu_{max.}$ 1 710 and 1 650 cm^{-1} (C=O); $\lambda_{max.}$ 276 nm (ε 7 400); δ($CDCl_3$) 2.52 (4 H, m, CH_2NCH_2), 3.40 (3 H, s, NMe), 3.47 (2 H, s, CH_2), 3.65 (3 H, s, NCH_3), and 3.68 (4 H, m, CH_2OCH_2).

1,3-Dimethyl-6-(N-methylanilino)methyl-5-nitrouracil (13c).—To a solution of the 5-nitrouracil (4) (1.4 g, 0.005 mol) in ethyl acetate (25 ml) was added *N*-methylaniline (1.07 g, 0.01 mol) with stirring and the mixture was stirred at room temperature for 4 h. The solvent was evaporated off *in vacuo* and to the residue was added ether. The precipitate was filtered off, washed with water, and dried to give the *6-(N-methylanilino)methyluracil* (13c) (1.4 g, 92%). Recrystallization from ethanol afforded yellow plates, m.p. 151—152 °C (Found: C, 55.2; H, 5.3; N, 18.5. $C_{14}H_{16}N_4O_4$ requires C, 55.25; H, 5.3; N, 18.4%); $\nu_{max.}$ 1 720 and 1 660 cm^{-1} (C=O); $\lambda_{max.}$ 245 and 278 nm (ε 15 900 and 10 100); δ($CDCl_3$) 2.85 (3 H, s, NMe), 3.40 (3 H, s, NMe), 3.48 (3 H, s, NMe), 4.30 (2 H, s, CH_2), and 7.00 (5 H, m, aromatic).

6-Acetoxymethyl-1,3-dimethyl-5-nitrouracil (13d).—To a solution of the 5-nitrouracil (4) (1 g, 0.0036 mol) in dimethylformamide (5 ml) was added a solution of sodium acetate (0.5 g, 0.0036 mol) in water (1 ml) with stirring at room temperature. After stirring for 1 h, the mixture was diluted with ice–water (50 ml) and the solution was extracted with chloroform. The chloroform solution was dried and evaporated to give the *6-acetoxymethyluracil* (13d) (0.65 g, 70%). Recrystallization from propan-2-ol afforded yellow needles, m.p. 89—89.5 °C (Found: C, 41.9; H, 4.35; N, 16.4. $C_9H_{11}N_3O_6$ requires C, 52.05; H, 4.3; N, 16.35%); $\nu_{max.}$ 1 760, 1 720, and 1 660 cm^{-1} (C=O); $\lambda_{max.}$ 280 and 330 (ε 6 100 and 3 600); δ($CDCl_3$) 2.12 (3 H, s, COMe), 3.38 (3 H, s, NMe), 3.55 (3 H, s, Me), and 5.20 (2 H, s, CH_2).

1,3-Dimethyl-6-(α-methylhydrazino)methyl-5-nitrouracil (14).—To a solution of the 5-nitrouracil (4) (1.4 g, 0.005 mol) in ethyl acetate (30 ml) was added dropwise methylhydrazine (0.46 g, 0.01 mol) with stirring in an ice-bath. Stirring was continued for 1 h, the mixture was filtered,

and the filtrate was evaporated *in vacuo* at room temperature. To the residue was added water and the precipitate was collected and dried to give the 6-(α-*methylhydrazino*)*methyluracil* (14) (0.56 g, 46%). Recrystallization from propan-2-ol afforded yellow needles, m.p. 126—127 °C (Found: C, 39.75; H, 5.3; N, 28.55. $C_8H_{13}N_5O_4$ requires C, 39.5; H, 5.4; N, 28.8%); $\nu_{max.}$ 3 360 (NH_2), and 1 710 and 1 650 cm^{-1} (C=O); δ($CDCl_3$) 2.63 (3 H, s, NMe), 2.93 (2 H, br, NH_2), 3.42 (3 H, s, NMe), and 3.68 (5 H, s, CH_2 and NMe).

Reaction of the Hydrazino-derivative (14) *with Benzaldehyde*.—A mixture of the 6-(α-methylhydrazino)methyluracil (14) (0.49 g, 0.002 mol) and benzaldehyde (0.21 g, 0.002 mol) in ethanol (15 ml) was refluxed for 15 min. After cooling, the resulting precipitate was collected to give 6-(2-*benzylidene*-1-*methylhydrazino*)*methyl*-1,3-*dimethyl*-5-*nitrouracil* (0.4 g, 61%). Recrystallization from ethanol afforded yellow needles, m.p. 155—156 °C (Found: C, 54.5; H, 5.15; N, 20.95. $C_{15}H_{17}N_5O_4$ requires C, 54.35; H, 5.15; N, 21.15%); $\nu_{max.}$ 1 720 and 1 660 cm^{-1} (C=O); $\lambda_{max.}$ 285 nm (ε 16 600); δ($CDCl_3$) 2.91 (3 H, s, NMe), 3.41 (3 H, s, NMe), 3.64 (3 H, s, NMe), 4.36 (2 H, s, CH_2), and 7.40 (6 H, m, CH=N and aromatic).

6-*Hydrazonomethyl*-1,3-*dimethyluracil* (15a).—(*a*) A mixture of the 6-(α-methylhydrazino)methyluracil (14) (0.234 g, 0.001 mol) and hydrazine hydrate (0.1 g, 0.002 mol) in methanol (5 ml) was refluxed for 30 min. After cooling, the resulting precipitate was collected by filtration to give the *hydrazone* (15a) (0.14 g, 76%). Recrystallization from methanol afforded pale yellow needles, m.p. 232—233 °C (Found: C, 46.2; H, 5.45; N, 30.9. $C_7H_{10}N_4O_2$ requires C, 46.15; H, 5.5; N, 30.75%); $\nu_{max.}$ 3 360 and 3 180 (NH_2), 1 680 and 1 640 cm^{-1} (C=O); $\lambda_{max.}$ 223, 282, and 324 nm (ε 7 100, 10 100, and 12 300); δ[$(CD_3)_2SO$] 3.17 (3 H, s, NMe), 3.41 (3 H, s, NMe), 5.78 (1 H, s, H-5), 7.53 (1 H, s, CH=N), and 8.02 (2 H, br, NH_2).

(*b*) Similar procedures to those mentioned above using (13b) and hydrazine hydrate afforded the hydrazone (15a) in 82% yield.

(*c*) Similar procedures to those mentioned above using (13c) and hydrazine hydrate afforded the hydrazone (15a) in 80% yield.

(*d*) A mixture of the 6-acetoxymethyluracil (13d) (0.51 g, 0.002 mol) and hydrazine hydrate (0.2 g, 0.004 mol) in ethanol (15 ml) was refluxed for 1 h. The solvent was evaporated off *in vacuo* and to the residue was added water. The precipitate was collected and dried to give the hydrazone (15a) (0.045 g, 12%).

(*e*) To a mixture of 6-hydrazonomethyluracil (0.154 g, 0.001 mol) in aqueous 5% NaOH (2 ml) was added dimethyl sulphate (0.28 g, 0.002 mol) with stirring at room temperature. Stirring was continued for 30 min, and the resulting precipitate was collected and dried to give the hydrazone (15a) (0.095 g, 52%).

6-(2-*Methylhydrazonomethyl*)-1,3-*dimethyluracil* (15b).—(*a*) To a solution of the 5-nitrouracil (4) (1.4 g, 0.005 mol) in ethyl acetate (25 ml) was added dropwise methylhydrazine (2.3 g, 0.05 mol) with stirring in an ice-bath. After stirring for 1 h, the mixture was filtered and the filtrate was evaporated *in vacuo* at room temperature. To the residue was added water and the precipitate was collected and dried to give the *methylhydrazone* (15b) (0.8 g, 83%). Recrystallization from methanol afforded yellow plates, m.p. 216—217 °C (Found: C, 48.9; H, 6.1; N, 28.75. $C_8H_{12}N_4O_2$ requires C, 48.95; H, 6.15; N, 28.55%); $\nu_{max.}$ 3 240 (NH) and 1 690 and 1 620 cm^{-1} (C=O); $\lambda_{max.}$ 222, 283, and 333 nm (ε 6 700, 10 100, and 16 300); δ[$(CD_3)_2SO$] 2.92 (3 H, d, NHMe), 3.18 (3 H, s, NMe), 3.48 (3 H, s, NMe), 5.80 (1 H, s, H-5), 7.03 (1 H, s, CH=N), and 8.70 (1 H, br, NHMe).

(*b*) Similar procedures to those mentioned above using the 6-(α-methylhydrazino)methyluracil (14) (0.12 g, 0.0005 mol) and methylhydrazine (0.046 g, 0.001 mol) afforded the methylhydrazone (15b) in 38% yield.

(*c*) A mixture of the 6-morpholinomethyluracil (13b) (0.45 g, 0.0016 mol) and methylhydrazine (0.2 g, 0.04 mol) in methanol (10 ml) was refluxed for 30 min. After cooling, the resulting precipitate was collected by filtration to give the methylhydrazone (15b) (0.3 g, 96%).

(*d*) A mixture of the 6-(*N*-methylanilino)methyluracil (13c) (0.3 g, 0.001 mol) and methylhydrazine (0.092 g, 0.002 mol) in methanol (5 ml) was refluxed for 1 h. After cooling, the resulting precipitate was collected by filtration to give the methylhydrazone (15b) (0.16 g, 82%).

(*e*) A solution of the 6-acetoxymethyluracil (13d) (0.51 g, 0.002 mol) and methylhydrazine (0.184 g, 0.004 mol) in methanol (15 ml) was refluxed for 1 h. The solvent was evaporated off *in vacuo* and to the residue was added water. The precipitate was collected and dried to give the methylhydrazone (15b) (0.11 g, 28%).

(*f*) To a mixture of the 6-(2-methylhydrazonomethyl)-uracil (0.168 g, 0.001 mol) in aqueous 5% NaOH (2 ml) was added dimethyl sulphate (0.28 g, 0.002 mol) with stirring at room temperature. Stirring was continued for 30 min, and the resulting precipitate was collected and dried to give the methylhydrazone (15b) (0.06 g, 31%).

6-*Phenyliminomethyl*-1,3-*dimethyluracil* (16a).—A mixture of the 6-(*N*-methylanilino)methyluracil (13c) (0.5 g, 0.0016 mol), aniline (0.16 g, 0.0017 mol) and triethylamine (1 ml) in absolute ethanol (15 ml) was refluxed for 1.5 h. The solvent was evaporated off *in vacuo* and to the residue was added ether. The precipitate was collected to give the 6-phenyliminomethyluracil (16a) (0.08 g, 21%). Recrystallization from light petroleum afforded pale yellow needles, m.p. 135—137 °C, identical with an authentic sample.[21]

6-(2-*Phenylhydrazonomethyl*)-1,3-*dimethyluracil* (16b).—A mixture of the 6-(*N*-methylanilino)methyluracil (13c) (0.3 g, 0.001 mol), phenylhydrazine (0.11 g, 0.001 mol), and triethylamine (0.5 ml) in absolute ethanol (10 ml) was refluxed for 1 h. After cooling, the resulting precipitate was collected by filtration to give the phenylhydrazone (16b) (0.13 g, 50%). Recrystallization from methanol afforded yellow needles, m.p. 244—245 °C, identical with an authentic sample.[21]

6-*Ethoxy*-(N-*methylanilino*)*methyl*-1,3-*dimethyluracil* (17).—A mixture of the 6-(*N*-methylanilino)methyluracil (13c) (0.61 g, 0.02 mol) and triethylamine (1 ml) in absolute ethanol (15 ml) was refluxed for 1 h. The solvent was evaporated off *in vacuo* and to the residue was added water. The precipitate was filtered off and dried to give the 6-ethoxy-(*N*-methylanilino)methyluracil (17) (0.35 g, 58%). Recrystallization from propan-2-ol gave plates, m.p. 136—138 °C, identical with an authentic sample.[21]

[1/998 *Received*, 19*th June*, 1981]

REFERENCES

[1] Part 40, K. Hirota, Y. Yamada, T. Asao, Y. Kitade, and S. Senda, *Chem. Pharm. Bull.*, 1981, **29**, 3060.

[2] A part of this work has been reported in preliminary communications: S. Senda, K. Hirota, T. Asao, and Y. Yamada, *J. Chem. Soc., Chem. Commun.*, 1977, 556; *Tetrahedron Lett.*, 1978, 2295.

[3] A. L. Pogolotti, jun., and D. V. Santi, ' Bioorganic Chemistry,' vol. I, ed. E. E. van Tamelen, Academic Press, New York, 1977, pp. 277—311.
[4] H. Hayatsu, *Prog. Nucleic Acid Res.*, 1976, **16**, 75; E. G. Sander, ' Bioorganic Chemistry,' vol. 2, ed. E. E. van Tamelen, Academic Press, New York, 1978, pp. 273—297.
[5] H. C. van der Plas, ' Ring Transformation of Heterocycles,' vol. 2, Academic Press, New York, 1973, pp. 116—146; S. Senda, K. Hirota, and K. Banno, *Tetrahedron Lett.*, 1974, 3087; K. Hirota, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, 1978, **43**, 1193; S. Senda, K. Hirota, T. Asao, and Y. Abe, *Heterocycles*, 1978, **9**, 739; K. Hirota, Y. Kitade, S. Senda, M. J. Halat, K. A. Watanabe, and J. J. Fox, *J. Am. Chem. Soc.*, 1979, **101**, 4423; K. Hirota, Y. Kitade, and S. Senda, *Heterocycles*, 1980, **14**, 407; K. Hirota, Y. Kitade, and S. Senda, *J. Heterocycl. Chem.*, 1980, **17**, 413.
[6] W. Pfleiderer and H. Mosthaf, *Chem. Ber.*, 1957, **90**, 728.
[7] H. U. Blank, I. Wempen, and J. J. Fox, *J. Org. Chem.*, 1970, **35**, 1131.
[8] I. H. Pitman, M. J. Cho, and G. S. Rork, *J. Am. Chem. Soc.*, 1974, **96**, 1840.
[9] K. Hirota, Y. Yamada, T. Asao, and S. Senda, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1896.
[10] E. C. Taylor and E. E. Garcia, *J. Org. Chem.*, 1965, **30**, 655; S. Senda and K. Hirota, *Chem. Pharm. Bull.*, 1974, **22**, 2593; S Nishigaki, Y. Kanamori, and K. Senga, *ibid.*, 1980, **28**, 1636.
[11] F. L. Rose, *J. Chem. Soc.* (*C*), 1952, 3448; *ibid.*, 1954, 4116
[12] K. Auwers and F. Niemeyer, *J. Prakt. Chem.*, 1925, **110**, 153.
[13] F. Lingens and H. Schneider-Bernlöhr, *Justus Liebigs Ann. Chem.*, 1965, **686**, 134; D. H. Hayes and F. Hayes-Baron, *J. Chem. Soc.* (*C*), 1967, 1528.
[14] For a survey of methods for the synthesis of pyrazolo[4,3-*d*]-pyrimidines, see R. K. Robins, F. W. Furcht, A. D. Grauer, and J. W. Jones, *J. Am. Chem. Soc.*, 1956, **78**, 2418; L. B. Townsend, R. A. Long, J. P. McGraw, D. W. Miles, R. K. Robins, and H. Eyring, *J. Org. Chem.*, 1974, **39**, 2023, and references cited therein.
[15] V. Papesch and R. M. Dodson, *J. Org. Chem.*, 1965, **30**, 199.
[16] A. R. Katritzky and J. M. Lagowski, ' Chemistry of the Heterocyclic *N*-Oxides,' Academic Press, London and New York, 1971, p. 258.
[17] The pyrimido[5,4-*d*]pyrimidine ring system has been synthesised in conjunction with the studies of coronary vasodilative activity, but the principal synthetic method involves condensation of 5-amino-4-carboxypyrimidines with C—N (C—N—C) fragment reagents; R. Kadatz, *Arzneim.-Forsch.*, 1959, **9**, 39; F. G. Fischer and J. Roch, *Justus Liebigs Ann. Chem.*, 1951, **572**, 217.
[18] It is known that azahexatrienes undergo thermochemical intramolecular cycloaddition to six-membered heterocycles: F. Yoneda, M. Higuchi and T. Nagamatsu, *J. Am. Chem. Soc.*, 1974, **96**, 5607; F. Yoneda and M. Higuchi, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1336; K. Senga, J. Sato, Y. Kanamori, M. Ichiba, S. Nishigaki, M. Noguchi, and F. Yoneda, *J. Heterocycl. Chem.*, 1978, **15**, 781; S. Nishigaki, J. Sato, K. Shimizu, K. Furukawa, K. Senga, and F. Yoneda, *Chem. Pharm. Bull.*, 1980, **28**, 142.
[19] N. Finch and H. W. Gschwend, *J. Org. Chem.*, 1971, **36**, 1463.
[20] K.-Y. Zee-Cheng and C. C. Cheng, *J. Heterocycl. Chem.*, 1967, **4**, 163.
[21] K. Hirota, Y. Yamada, Y. Kitade, and S. Senda, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2943.
[22] E. C. Taylor, F. Sowinski, T. Yee, F. Yoneda, *J. Am. Chem. Soc.*, 1967, **89**, 3369; Y. Maki, K. Izuta, and M. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1971, 1442; *Tetrahedron Lett.*, 1972, 1973; Y. Maki, M. Auzuki, K. Izuta, and S. Iwai, *Chem. Pharm. Bull.*, 1974, **22**, 1269; Y. Maki, T. Hiramitsu, and M. Suzuki, *ibid.*, 1974, **22**, 1265; S. Senda, K. Hirota, M. Auzuki, and M. Takahashi, *ibid.*, 1977, **25**, 563.